A review on the use of minerals in the treatment of COVID-19

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelors of Pharmacy

Department of Pharmacy
Brac University
November 2021

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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of Spring, 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on [Date-of-Defense].

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Ethics Statement

The thesis was done without unethical work. No human or animal tests are involved in this study.

Abstract

Since the advent of Covid 19 in December 2019, researchers have been conducting studies to determine different techniques for treatment and prevention. The usage of minerals for the possibly prevent and cure Covid-19 has been investigated in this study. The information was gathered from a variety of publications, research articles, WHO guidelines and interviews. Since its inception, the disease has produced varied degrees of illness in a variety of people. A generalization of patients was undertaken, and the potential influence of minerals to help in therapy was also investigated. It is known that both mineral deficiencies and excesses in the body assist in disease. As a result, a healthy balance should be maintained at all times. Readers should be aware that because Covid is a burning issue, new data is updated practically every hour.

Keywords: SARS-CoV-2, prevention, vaccine, treatment, spike protein, immunity.

Acknowledgement

First and foremost, I would like to start by expressing my heartfelt gratitude to Allah (SWT) for showering me with numerous benefits and allowing me to finish the thesisI'd want to express my heartfelt gratitude to everyone for their advice and assistance.

I'd want to convey my heartfelt appreciation for my project, as well as the academic supervisor's valuable supervision and enthusiasm, Shahana Sharmin (Assistant Professor, Department of Pharmacy, Brac University).

I would also want to thank Dr. Hasina Yasmin (Professor, Department of Pharmacy, Brac University) for her commitment, contribution, and direction to both the student and the department.

I am also thankful to Professor Dr. Eva Rahman Kabir, Honorary Chairperson, Department of Pharmacy, Brac University for her assistance with my project work and for allowing me to complete my B.Pharm program.

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List of Acronyms

APCs	Antigen Presenting Cells
ARD	Acute Respiratory Disorder
COPD	Chronic obstructive pulmonary disease
WHO	World Health Organization
RDA	Recommended Daily Allowance
ROS	Reactive Oxygen Species

Chapter 1

1.1 Introduction

From the dawn of humanity, human kind had to face a lot of challenges. One of the major challenges that humanity faced and still face is preserving good health. According to WHO [1], Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Diseases, on the other hand, are defined as any adverse deviation from an organism's natural structural or functional state, which is usually accompanied by certain signs and symptoms and ranges from natural physical injuries. [2]. Many diseases have haunted humans from the earliest of ages and even in this modern age many diseases, both new and old, prevail. But very few have marked the 21st century as the Coronavirus or COVID-19.

1.2 Background

On December of 2019 a new disease was discovered in Wuhan, China caused by a new strain of virus named 2019 novel coronavirus and the disease was named Novel Coronavirus-Infected Pneumonia which was later named Covid-19 (corona virus disease 2019 [3]. Covid-19 is a highly infectious disease which soon became pandemic forcing the whole world to go into

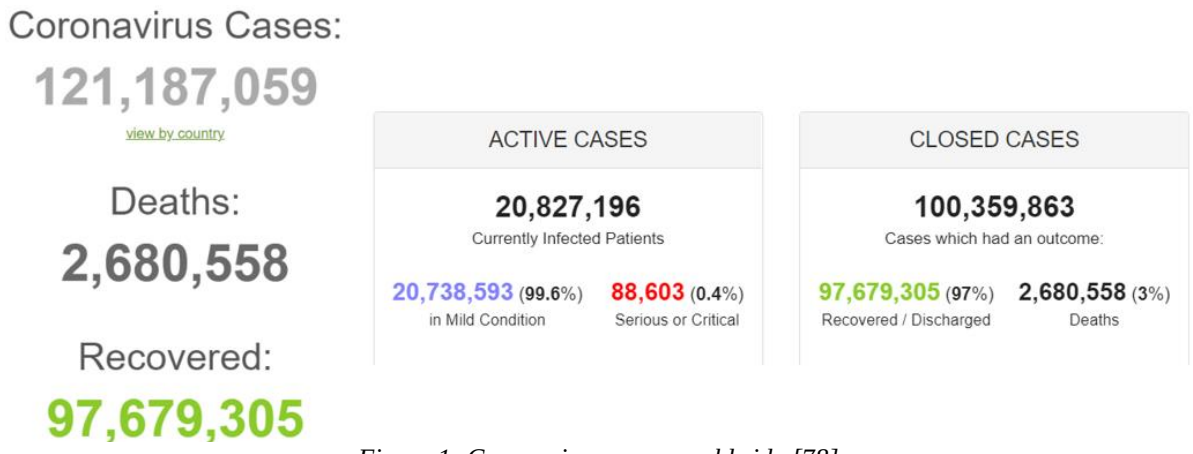

Figure 1: Coronavirus cases worldwide [78]

quarantine. Since its discovery, almost every country has been infected by this virus. According to Worldometer.info there are 121,187,059 covid cases worldwide. Currently 30,183,243

active cases of Covid-19 in U.S.A. 11,594,204 in Brazil, 11,438,464 in India and 560,887 in Bangladesh. Covid-19 belongs to the large group of RNA viruses called Coronavirus. Coronaviruses are prevalent viruses that cause nasal, sinus, and upper throat infections. The vast majority of coronaviruses are not particularly dangerous [4].

Coronaviruses are enveloped viruses that encode at least three types of proteins: membrane

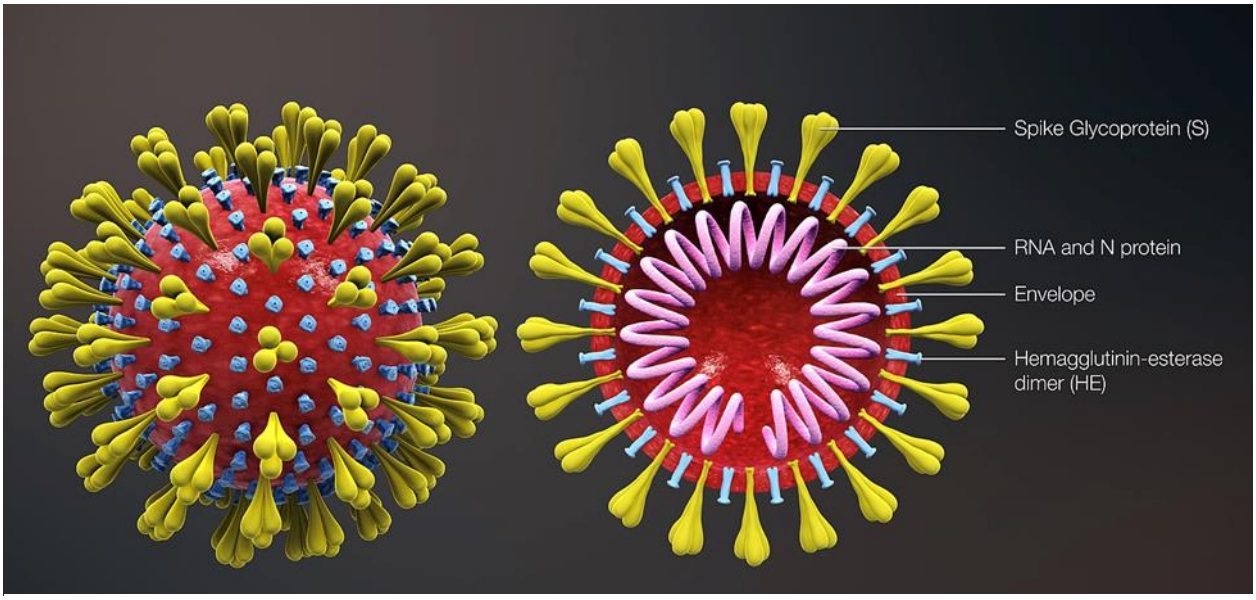

Figure 2: A structure of Respiratory Syndrome coronavirus. [85]

proteins (M), spike proteins (S), and envelope proteins (E). These proteins interact with the host cell's secretory system to enable the virus to biosynthesise required components. Other than the afore mentioned proteins, group 2 coronaviruses have another envelop protein called hemagglutinin-esterase (HE) protein. The nucleocapsid (N) protein is another structural protein and this encapsidates the RNA genome of the virus. Coronaviruses assemble by budding into the lumen of a dynamic intermediate compartment complex of endoplasmic reticulum and Golgi (ERGIC). The viral nucleocapsid interacts with the M protein ultimately causing virion development by budding into the ERGIC lumen. Exocytosis is used by the infected cells to release the virions that have been created [5]. These viruses are known as coronaviruses because of their virions, which resemble crowns and surround the envelop. Other than Covid-

19 other significant diseases caused by this family of viruses are Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

1.3 Coronavirus Evolution

Tyrrell and Bynoe identified the first coronavirus in humans in 1965 from nasal washings of a boy suffering from common cold symptoms and named the virus B814. In 1966, Hamre and Procknow isolated a novel respiratory virus from the respiratory tract of a medical student with a cold. They named this strain 229E. Following that, in 1967, scientists at the National Institutes of Health in Bethesda isolated morphologically similar viruses by organ culture and named them OC38 and OC43 [6]

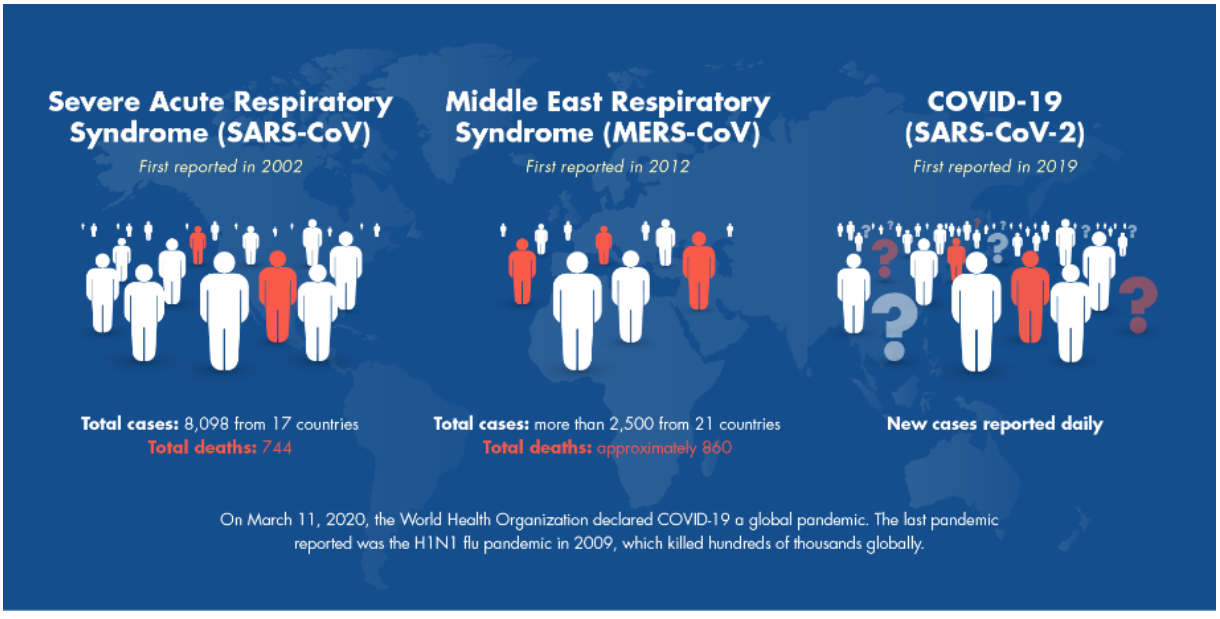

Figure 3: Cases of recent corona virus outbreaks [7]

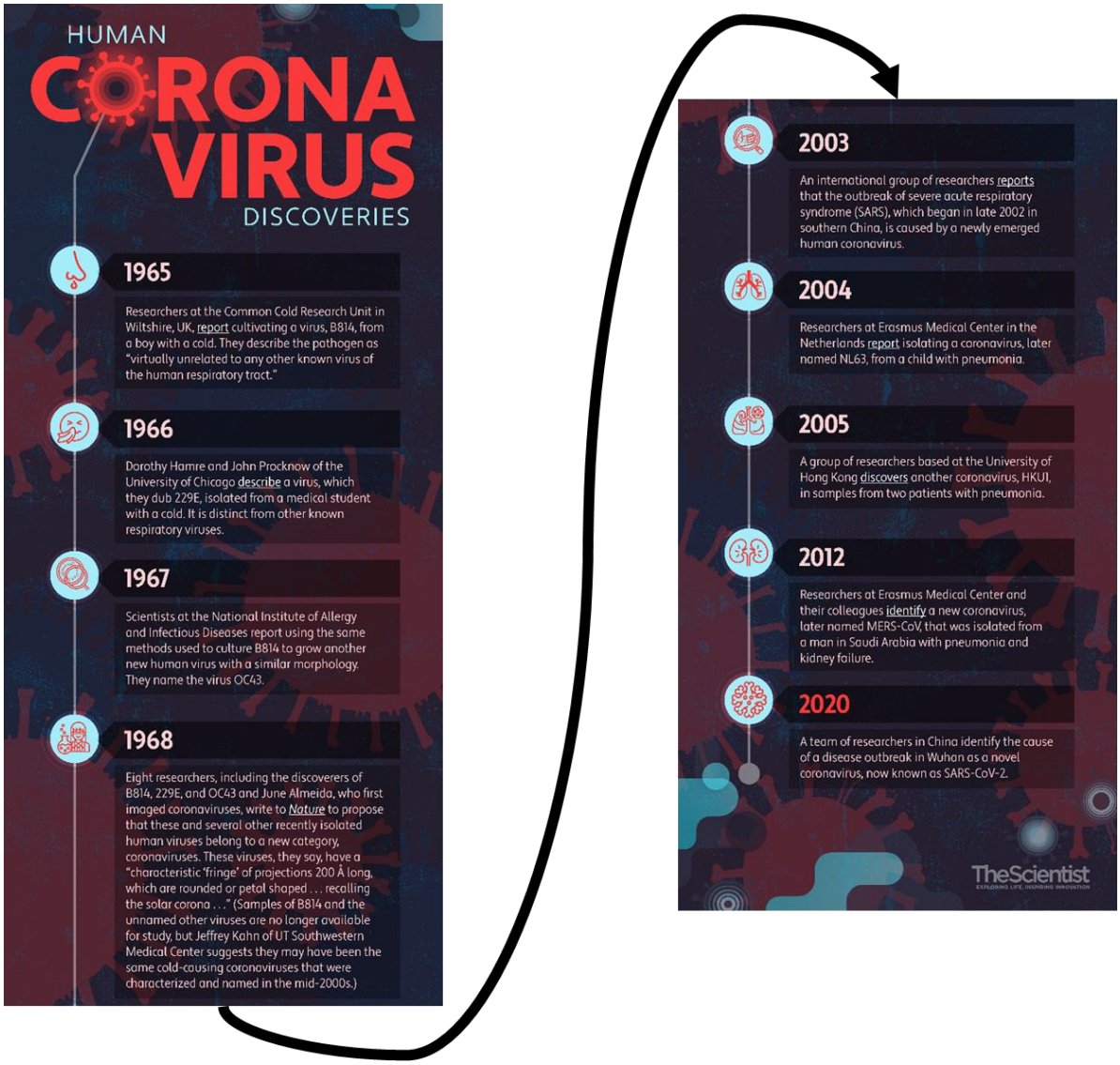

Figure 4: History of Human Coronavirus

There are currently seven coronaviruses that can infect humans. MERS (2012) and SARS (2002) are two other recent coronavirus outbreaks, in addition to Covid-19. A total of 8,098 SARS cases were registered in 17 countries, with a fatality rate of 11%. About 2,500 MERS cases have been registered in 21 countries, resulting in approximately 860 deaths [7].

SARS is a coronavirus that emerged in southern China and causes fever, headaches, and coughing and shortness of breath. MERS, on the other hand, emerged in Saudi Arabia and has similar respiratory symptoms to SARS, but it can also result in kidney failure [8].

The coronaviruses that caused Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), according to scientists, appeared in bats, and SARS-CoV-2 is

also believed to have originated from bats. It is speculated that the SARS-CoV-2 virus came from one of Wuhan's open-air “wet market”. Viruses may adapt to their surroundings in order to survive in other species, and crowded areas are optimal for cross-species transmission. However, during the outbreak, the Wuhan market did not sell bats. As a result, there was early suspicion on scaly anteaters, also known as pangolins, which were sold in the market. Additionally, the coronaviruses that infect pangolins have been discovered to be comparable to SARS-CoV-2 [8].

We all know viruses are highly prone to mutation, and the coronavirus is no exception. The strain of Covid-19 has undergone several mutations and it is different for each country. According to WHO, two specific variants of SARS-CoV-2 have been identified as of now. They were registered in the United Kingdom and South Africa, respectively. Despite the fact that the variants differ, the N501Y mutation has been identified as a common mutation between them. These variants are much more infectious than the previous SARS-CoV-2 strain [9]. The latest strain discovered in the UK is known as B.1.1.7, and it has been identified in many countries around the world, including the United States of America, Bangladesh, and others. When compared to other variants, this strain has a greater chance of causing death in humans. The South African variant, also known as B.1.351, has demonstrated little significant change in disease severity and has been found in Zambia and the United States [10].

Aside from these two variants, another notable SARS-CoV-2 variant is P.1, which branched off the Japanese B.1.1.28 lineage. This variant, which can now also be found in the United States, was first reported in Brazil. The P.1 lineage features three variations in the spike protein receptor binding site, which could render the strain immune to vaccines and antibodies produced from prior exposure [10].

Apart from the aforementioned variants, there are several other SARS-CoV-2 variants, including the Californian variants, also known as B.1.427 and B.1.429. Constant research is being conducted as new strains are identified from around the world. These new variants have not yet shown any significant change in disease severity, but the majority are more contagious [11].

The viral SARS-CoV-2 pathogen is constantly evolving and as a result constant monitoring is essential because the variants may [10]:

- Become more contagious and rapidly infect individuals
- Vary in their potential to produce either lesser or more serious disease.
- Avoid being detected in viral diagnostic tests
- Reduced sensitivity to therapeutics
- Avoid naturally occurring or vaccine-induced immunity

Since the SARS-CoV-2 pathogen is rapidly evolving and the consequences are unpredictable, it is much easier to be cautious and take preventive measures against the virus.

1.4 Transmission of Covid-19

Before we can take some practical prevention measures, we must first understand how the virus spreads. COVID-19 is a highly infectious virus that spreads by droplets formed by an infected person's respiratory system and released into the air by coughing, sneezing, and other respiratory behaviors. The virus may also be spread by surface contamination, which happens when these droplets fall on items and surfaces another person touches these objects or surfaces, and after that touches their eyes, nose, or mouth. Furthermore, since the virus is found to be present in feces, someone who does not properly wash their hands after using the toilet or

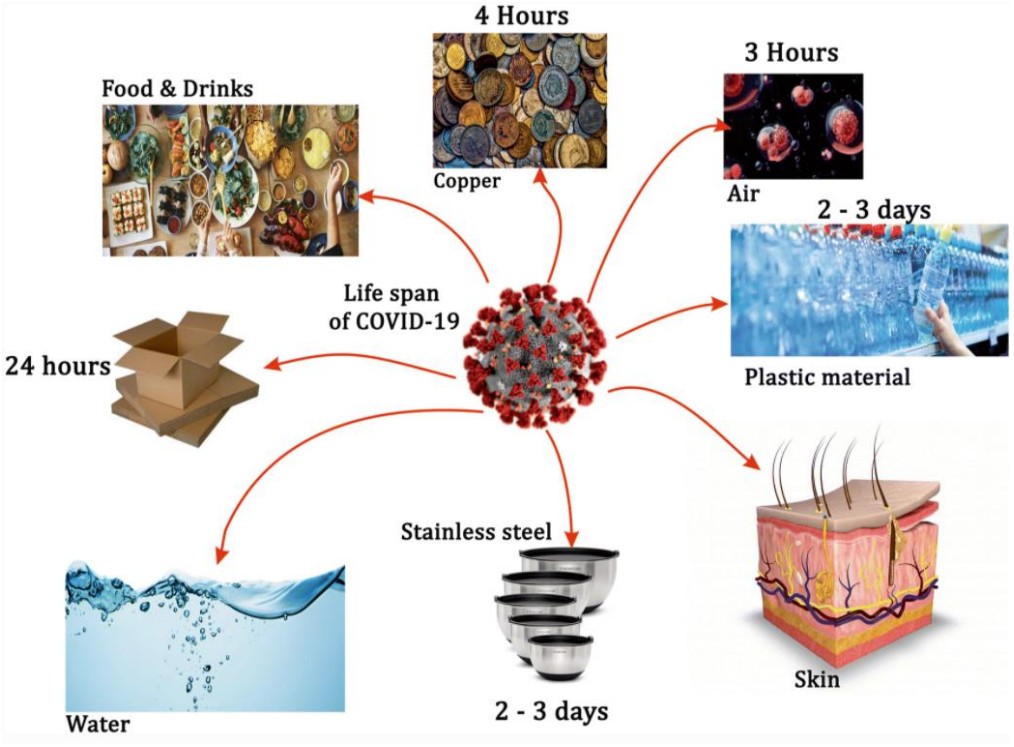

Figure 5: Virus resilience on various surfaces and materials [12]

bathroom will contaminate things they touch [3]. According to one study, SARS-CoV-2 will live for several hours on a variety of surfaces. The virus can survive on copper for 4 hours, cardboard for up to 24 hours, and plastic and stainless steel for up to 2 to 3 days [4]. Due to ethical reasons virus resilience on skin cannot be researched. And thus far, there seems to be no evidence of the virus spreading by food, alcohol, soda, juice or water. And if an individual swims, he may not become infected from the water; but, if the pool or lake is crowded, he might become infected [12]. In crowded locations, close contact between individuals, and tight

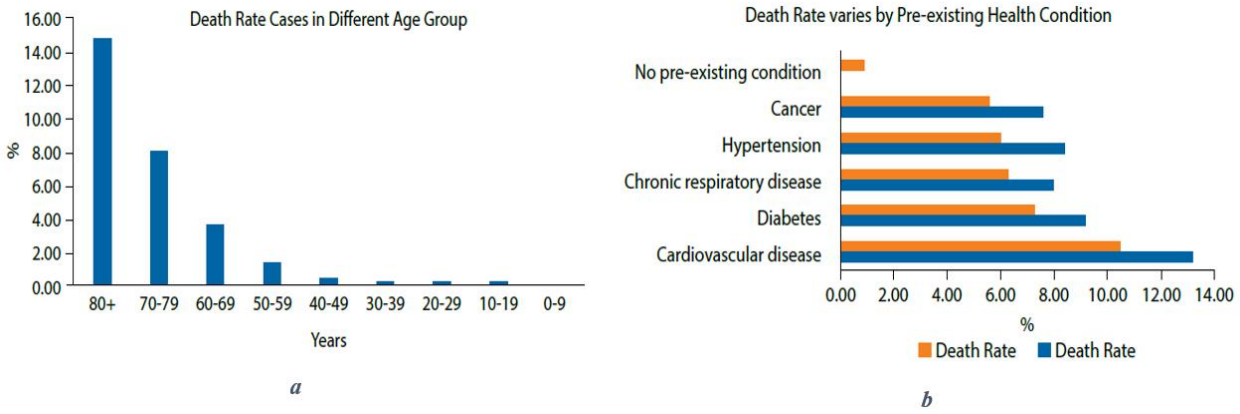

Figure 6: a) Covid-19 death Rate by Pre-Existing health conditions. b) Covid-19 death Rate by Pre-Existing health conditions [3]

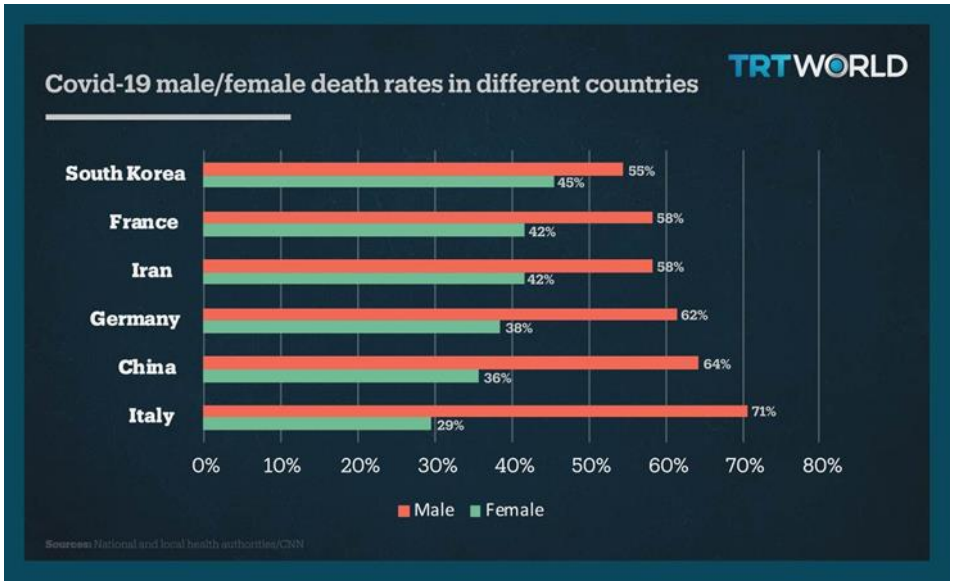

Figure 7: Covid-19 death Rate by Sex Ratio [86]

spaces with poor ventilation, the risk of viral transmission increases dramatically [13]. Temperature and humidity have also been shown to have an effect on disease transmission. According to one report, a 1°C increase in temperature reduces daily new cases by 3.08% and the daily death rate by 1.19%. In the same report, it was discovered that rising relative humidity by 1% lowered daily new cases by 0.85% and daily death rate by 0.51% [14]. The disease's mortality rate is influenced by age, race, and pre-existing medical conditions. The death rate increases with age, with children under the age of nine seemingly unaffected, but infected people above the age of 80 having a 14.8 % mortality rate. Although the cause is unknown, infected males have a higher fatality rate than females, with the ratio varying by country. Pre-existing medical conditions also greatly raise the risk of death [3].

1.5 Disease Progression

Infection begins as the virus enters the body and attaches to a target cell, an angiotensin converting enzyme 2 receptor. The virus enters the cell with the help of two spike protein subunits. Through the receptor-binding domain, the S1 subunit attaches the virus to the ACE2. Furthermore, the S2 subunit connects the viral cell with the host cell. [15]. Coronavirus RNA has a 3' polyadenylated tail and a 5' methylated head that binds to free ribosomes in the host

cell, causing translation and the formation of a long polypeptide chain. This polyprotein is broken down into several nonstructured proteins with a Proteases which helps with further penetration into the cell [3]. When a virus enters a cell, the body's natural antiviral defenses are triggered, and APCs (Antigen Presenting Cells) associate with the virus antigens.

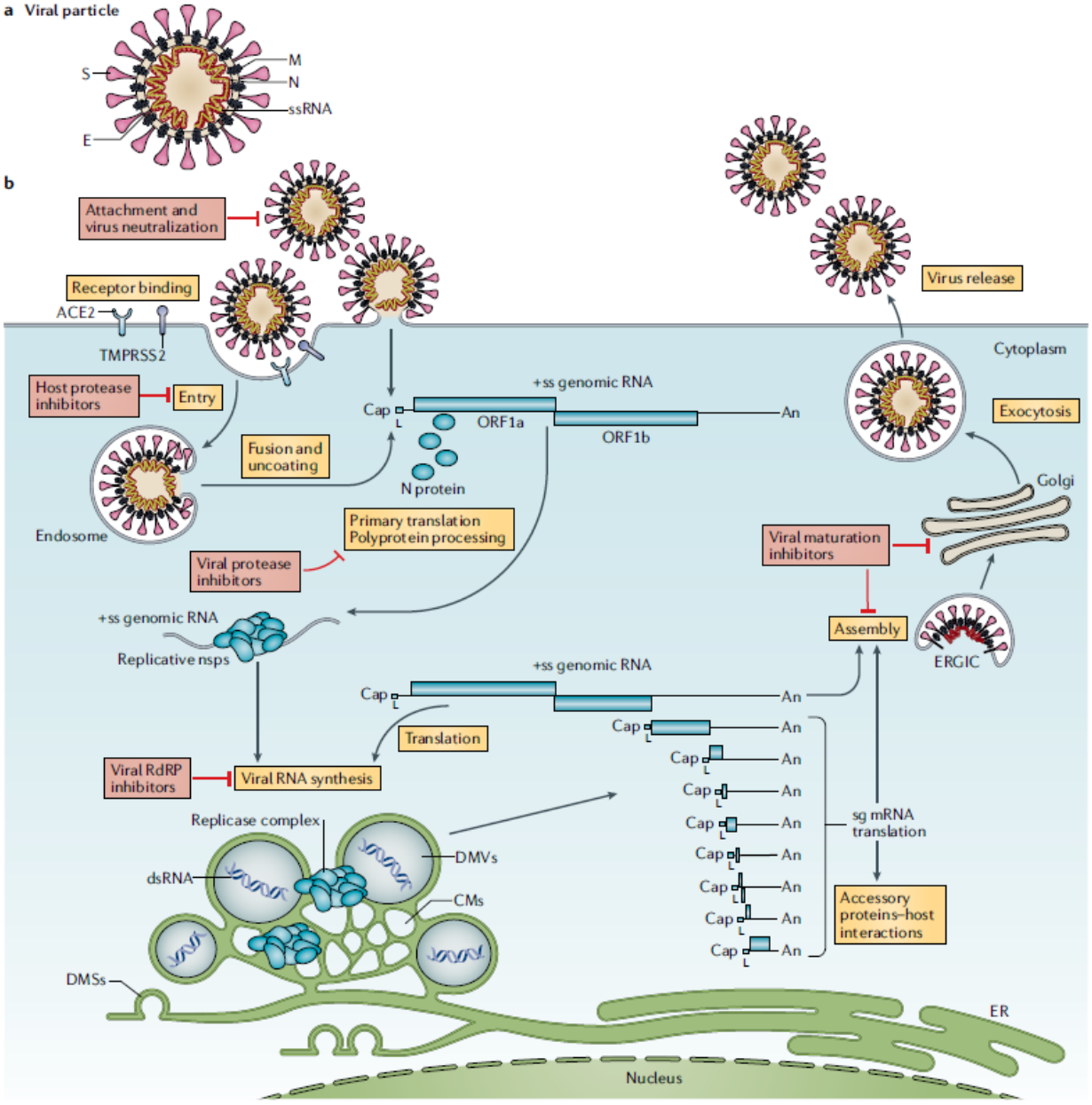

Figure 8:The coronavirus virion and life cycle [80]

The antigenic peptides stimulate both humoral and cellular immunity, which is regulated by virus-specific B-cells and T-cells. The infection has been shown to stimulate the development of virus-specific B-cells and T-cells. Moreover, it also stimulates the production of IgG and

IgM. The majority of the IgG antibodies generated are S-specific and N-specific antibodies, which are considered to have a greater preventative function. Furthermore, CD4+ and CD8+ T cells are overactivated, and CD4+ and CD8+ T memory cells live for 4 years without antigens, assisting with T cell proliferation, DTH reaction, and IFN-γ formation in case of future invasions [16]. The spike protein of SARS-CoV-2 viruses has a higher affinity for ACE2 than that of SARS-CoV viruses, which may explain some of the enhanced infectivity [17].

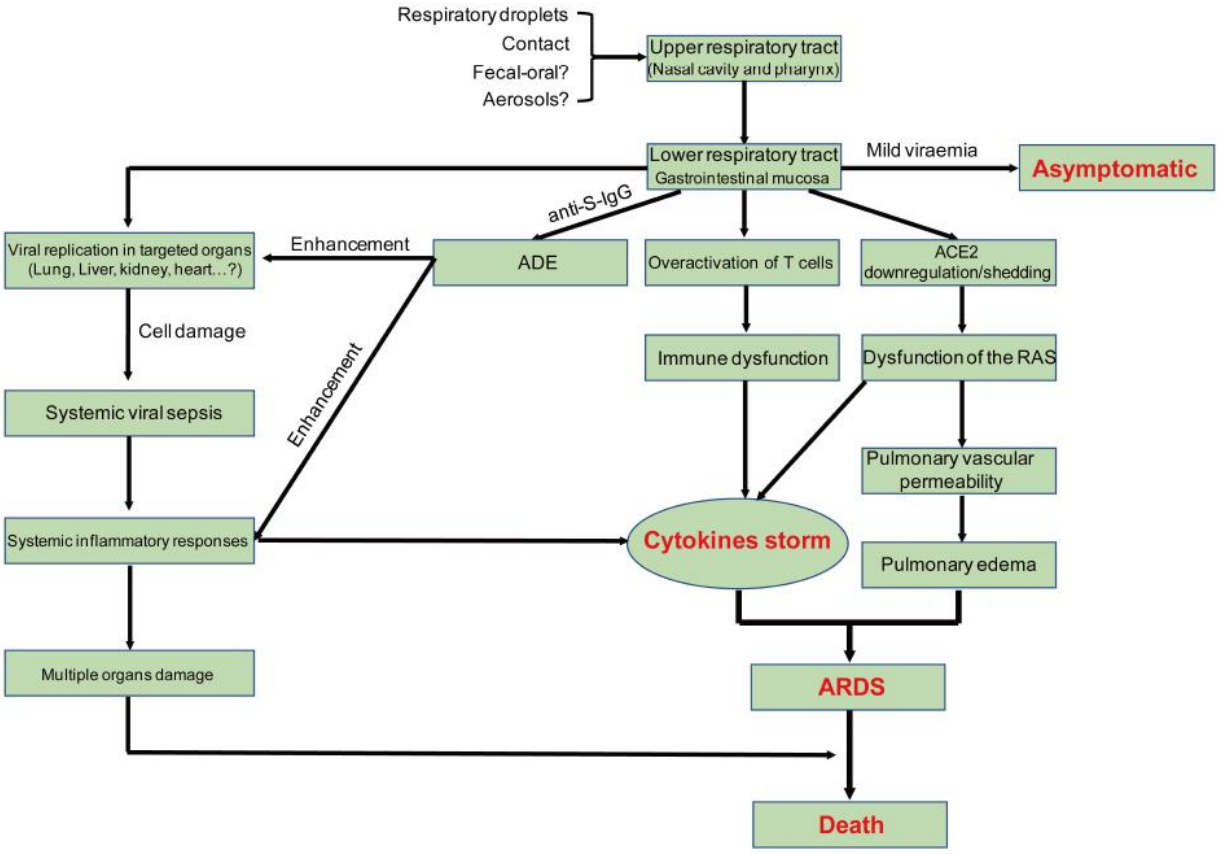

Figure 9: Postulated pathogenesis of SARS-CoV-2 infection. Antibody-dependent enhancement (ADE); ACE2: angiotensin-converting enzyme 2; RAS: renin-angiotensin system; ARDS: acute respiratory distress syndrome [81]

Based on recent data, signs and symptoms typically take two to 14 days after becoming infected [3]. It is not essential for every infected person to display symptoms; instead, they become virus carriers. These individuals are referred to as asymptomatic patients. Pre-symptomatic patients do not display symptoms at first, but they gradually develop them [13]. The most common cause of severe case or death from Covid-19 is ARD (Acute Respiratory Disorder) caused by a mechanism called cytokines storm, which triggers a deadly unregulated systemic

inflammatory response as a result of immune effector cells releasing massive quantities of pro-inflammatory cytokines (IFN-, IFN-, IL-1, IL-6, IL-12, IL-18, IL-33, TNF-, TGF, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) [16]. As per the Chinese CDC, 80% of all cases are minor, 15% are serious, and 5% are deadly serious The symptoms worsen with each passing day. A brief breakdown is given below [3].

Day 1: Patients experience fever, fatigue, muscle pain, and a dry cough on the first day of symptoms. Some patients develop nausea and diarrhea before experiencing any symptoms.

Day 5: Patients start to experience respiratory issues, which worsen in the elderly or asthmatic patients.

Day 7: Patients who have persistent symptoms like chest tightness, shortness of breath, bluish lips or face are admitted to the hospital on this day. Alternatively, the patients begin to feel better from their prior symptoms.

Day 8: According to the Chinese CDC, 15% of patients develop ARD (Acute Respiratory Disorder).

Day 10: If the disease condition progresses, the patient's symptoms intensify and he or she is admitted to the ICU.

Day 17: As the disease has a low mortality rate of around 3%, the majority of patients survive and are discharged from the hospital after two and a half weeks.

1.6 Risk Factors

Risk factors are those things that increases the probability of a disease developing in the person. A healthy lifestyle will act as countermeasure for the risk factors and may also mitigate some risks. The risk factors contributing to covid-19 are (Pathak, 2021):

- Age
- Chronic kidney disease
- Chronic obstructive pulmonary disease (COPD)
- Suppressed or compromised immune system due to surgeries like organ transplant or medications like corticosteroids
- Obesity
- Conditions such as heart failure or coronary artery disease
- Sickle cell disease
- Diabetes
- Moderate to severe asthma
- Cystic fibrosis
- High blood pressure
- Liver disease
- Pregnancy
- Pulmonary fibrosis
- Smoking
- Thalassemia
- Multisystem inflammatory syndrome in children

Chapter 2

2.1 Treatment

On March 11, 2020, WHO designated Covid a global pandemic, and since then, several pharmaceutical companies have been researching various ways to treat the disease. Initially, only symptomatic care was given, such as oxygenation, drainage, and fluid management. Treatment with low-dose systematic corticosteroids and antivirals, as well as atomization inhalation of interferon, has been recommended [18]. Vaccines to suppress the virus are currently being created. Since there is no cure, the therapeutic classes of medicines available for symptomatic therapy are anti-viral, anti-malarial, and herbal treatments [18]. Various combination therapies are now being used to treat the condition. As the old saying goes, prevention is better than cure, this is especially true when it comes to Covid. As a result, having a healthy lifestyle could be lifesaving. Some preventive measures advised by WHO includes washing one's hands with soap and sanitizer on a regular basis, wiping surfaces with disinfectants, keeping social distance, not touching one's face, and wearing masks in public spaces. Furthermore, having a strong immune system is critical for both preventing and treating the disease once infected. Having a healthy lifestyle along with some minerals and vitamins are crucial for boosting the immune system. A variety of trace elements, including copper, zinc, and selenium, have been shown to be essential for the proper functioning of the immune system.

2.2 Minerals

Minerals in health science are not rocks found can be on river or ocean coasts, but rather important nutrients for survival of living organisms. Not all minerals essential for life, and those that are not beneficial can be poisonous to humans. Human-required minerals are classified into two types: macro minerals and micro minerals (Trace Minerals) [19].

Macrominerals

The human body requires a higher concentration of certain elements. Macrominerals include calcium, phosphorus, magnesium, sodium, potassium, chloride, and sulfur.

Table 1: A table showing the recommended daily allowance (RDA), functions, sources, deficiency and excess effects.

Minerals	**RDA (mg)**	**Functions**	**Sources**	**Deficiencies**	**Excess**
Calcium	1000	• Improves bone and teeth health • Helps in muscle contraction and relaxation • Helps in conversion of various signals into biological effect. • Helps in action potential conduction	Milk, yogurt, cheese, kale, broccoli, and Chinese cabbage are the natural sources. Calcium supplements are used as artificial or synthetic sources	• Osteopenia • Osteoporosis	• Constipation. • May hinder absorption of iron & zinc. • Kidney stones

Phosphorus	700	• Bones and teeth formation. • Helps in ATP formation • Protein Synthesis	Fish, meat, eggs, grains, poultry,	• Loss of appetite • Bone pain	• Osteoporosis • May lead to calcium deposits. • Heart Attack • Stroke
Magnesium	320-420	• Helps with enzymatic activation.	Nuts, whole grains, fruits	• Muscle spasm • Irregular heartbeat	• Diarrhea
Sodium	>2300	• Maintain proper fluid balance • Nerve transmission • Muscle contraction	Table salt, canned & processed foods	• Hyponatremia	• Hypernatre-mia • High blood pressure
Potassium	4700	• Maintain proper fluid balance • Nerve transmission • Muscle contraction	Potatoes, prunes, tomatoes, bananas, beans	• high blood pressure • constipation • muscle weakness • fatigue	• Irregular heartbeat • Hyperkalem-ia

Chloride	800	• Maintain proper fluid balance • Formation of Gastric acid	Table salt, seaweed, rye, tomatoes, lettuce, celery, and olives	• Hypochlorem-ia	• excessive fatigue. • muscle weakness. • breathing problems. • frequent vomiting. • prolonged diarrhea. • excessive thirst. • high blood pressure
Sulfur	1000	• DNA maintenance • Assist in metabolization	Meat, poultry, fish, black beans, kidney beans, split peas	• Muscle spasm • Arthritis • Convulsion	• Flatulence • Potassium & calcium abortion decreased • Diarrhea

Trace Minerals

These minerals are only required by the body in trace amounts. Iron, zinc, iodine, selenium, copper, manganese, fluoride, chromium, and molybdenum are just a few examples of trace minerals.

Table 2: Table showing the recommended daily allowance (RDA), functions, sources, deficiency and excess effects

Minerals	RDA	Functions	Sources	Deficiencies	Excess
Iron	Male-8mg Female-18mg	• Needed for distribution of oxygen throughout the body • Essential component of hemoglobin	Red meats, fish, egg yolk, dark leafy greens, poultry and liver	• Iron deficiency anaemia • Increased sensitivity towards infections	• Constipation • Increased susceptibility of heart disease.
Zinc	Male-11mg Female- 8mg	• Wound healing • Development of normal fetal	Meat, milk, cheese, eggs, shellfish, whole	• Increased sensitivity towards	• Decreased T-cell proliferation • Decreased antibody

		• Helps with T-cell maturation • Helps with cell division	grain cereals, nuts and pulses.	infections • Decreased T-cell function • Reduced antibody responses	production • Disruption of copper metabolism
Iodine	150µg	• Necessary component of thyroid hormone.	Seafood, iodized salt, bread, dairy products	• Lethargy • Swelling of the thyroid gland • Goiter • Infants with cretinism.	• May cause thyroid problems.

Selenium	55µg	• Important part of glutathione peroxidase	Brazil nuts, bread, fish, meat and eggs	• Oxidative stress • Lowered resistance towards infections • Keshan disease • Decreased antibody production • Impaired lympho-proliferative responses	• Brittle nails and hair • Skin lesions • Garlic odour on the breath • Gastro-intestinal upsets
Copper	900µg	• Helps in formation of RBC • Helps with iron absorption	Shellfish, liver, kidney, nuts and whole grain cereals	• More prone to parasitic, bacterial, and viral infection • Lympho-proliferative responses reduced • Anemia	• Wilson disease • Hepatitis • Kidney problems • Brain disorders

				• Osteoporosis	
Manganese	Male- 2.3mg Female- 1.8mg	• Helps to maintain bone tissue • Helps with various enzyme activation	Tea, vegetables cereals and nuts.	•	•
Fluoride	Male- 4mg Female- 3mg	• Helps maintain healthy teeth & bone.	Water, fish, tea, coffee.	• Increased risk of dental carries	• Decay of teeth • Discoloration of teeth
Chromium	Male- 35µg Female- 25µg	• Carbohydrate and lipid metabolism • Promote the action of insulin	Meat, nuts, cereal grains, brewer's yeast and molasses	• Impaired glucose tolerance • Insulin resistance • Diabetes	• Skin lesions
Molybdenum	45µg	• Essential co-factor for some enzymes	Legumes, breads, grains, leafy	• intellectual disability • seizures	• Gout like symptoms.

			greens, milk, liver	• opisthotonos • lens dislocation.	

2.3 Impact of minerals on covid-19

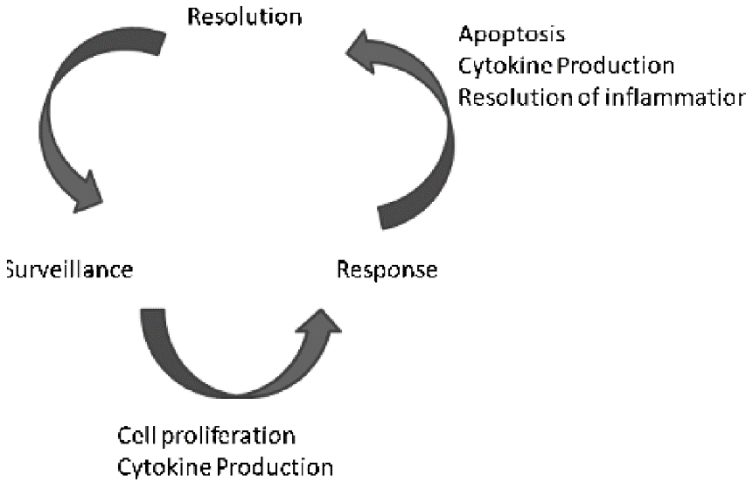

Figure 10: The cyclic nature of immunity [21]

Human immune system is a complicated and inefficient mechanism which necessitates regular consumption of most nutrients in order to operate effectively. With age, the functioning of the immune system is reduced. It is probably a cause of different diseases in the elderly. Nutritional intervention is therefore necessary to strengthen the immune system or avoid its deterioration [20]. An immune response is divided into three stages: surveillance, response, and response termination. The cells require more nutrients during the reaction necessary for cell growth and mediator production. Chronic inflammation occurs when the cell response does not terminate, and it may cause diseases. The gamma delta Tcells (γδ T cells) are a kind of T cell are crucial as a pathogen elimination's initial line of defense and also to end the immune response when it is not required. Vitamins and minerals, for example, can help γδ T cells mature, increasing their efficiency at pathogen elimination. According to certain study, when people ingest these

chemicals, cells can participate in replication more frequently; moreover, the intensity of cold and flu symptoms is reduced. Prime γδ T cells can also help minimize chronic inflammation, reinforcing their dual functions. The immune system is supported by both vital nutrients and protective non-essential phytochemicals [21].

Zinc

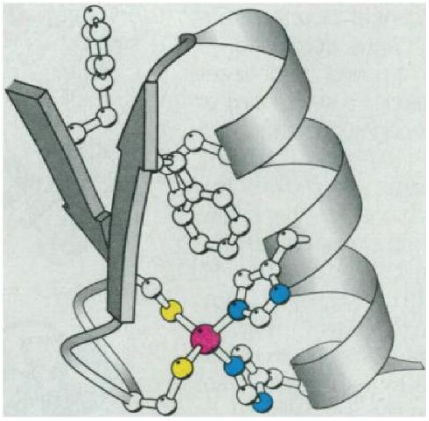

Figure 11: Schematic view of zinc finger present in major groove of DNA [24]

One of the most abundant trace minerals in the humans is zinc. As a result, several research have been made to determine zinc's biological purpose, and the first biological function was discovered in 1940 as a requirement for the catalytic action of carbonic anhydrase. In recent years, several more zinc-containing enzymes have been discovered. However, zinc deficiency does not render the enzymes ineffective or have little effect on catalytic activity; rather, allosteric regulation is lost. Other notable biological functions include DNA, RNA, and protein synthesis and stabilization. Zinc has also been proven to be important in cell development and differentiation, as well as antioxidant defense [22].

Enzymes are a collection of polypeptide chains made up of several long amino acid chains. The role of enzyme varies depending on the structure of the polypeptide chain. [23]. Polypeptides fold in different ways to achieve the desired domain. However, the chain must contain at least 50 amino acids in order to fold on its own. It has been observed that structure-stabilizing zinc cross-links are formed to form folds in smaller domains since zinc ions do not

add undesired chemical reactivity. In recent studies it has been observed that zinc helps in gene folding as well as other important enzymes. Zinc sometimes acts as a bridge between substrates and receptors and also has a role on various transcription factors such as TIFFA (protein transcription factor IIIA). Zinc finger proteins are zinc-based domains that can be of many kinds, such as RING finger protein, TFIIIA, and retroviral nucleocapsid, to mention a few. [24]

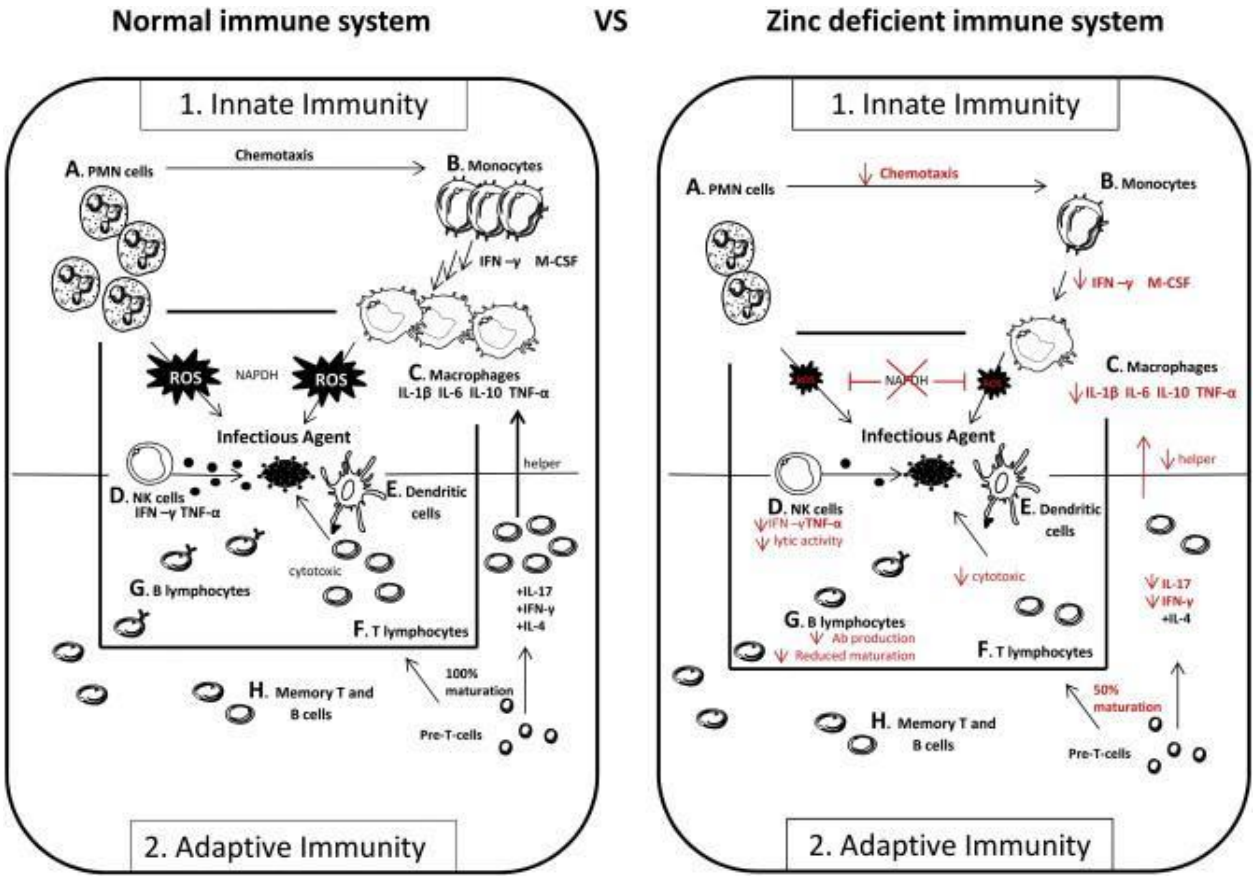

Figure 12: Zinc's function in inflammation and immunity [83]

In the United States, deficiency of zinc is a frequent dietary problem, and it has been related to illnesses such as alcoholism, renal failure, burns, gastrointestinal tract problems, and acrodermatitis enteropathica [25]. It may induce thymic involution and thymocyte depletion, as well as a decrease in DDH, T-lymphocyte quantity, T-cell mitogen responses, T helper function, natural killer function, and cytotoxic killer-cell function [20]. Zinc has been related to neutrophil, natural killer cell, T lymphocyte, B lymphocyte, and immunoglobulin G

development and maturation. Zinc deficiency has a negative impact on macrophages, resulting in dysregulated intracellular killing, cytokine formation, and phagocytosis. Furthermore, Zinc deficiency stimulates apoptosis [26]. Zinc deficiency can be treated by consuming zinc-rich foods like beef, milk, cheese, seafood, shellfish, whole grain cereals, nuts, and so on, or by taking zinc supplements. Taking zinc supplements would usually be sufficient to overcome the symptoms of zinc deficiency. Zinc supplements can be used orally, intramuscularly, or intravenously, and can be taken in single or separated doses. Zinc RDAs are around 2mg for children under the age of six months, 11mg for men, and 8mg for females over the age of thirteen. The tolerable upper limit (TUL) for zinc is 7mg for children aged 1-3 years and 25mg for adults and females of any age who are pregnant or breastfeeding [27]. Zinc deficiency in pregnant women can cause intra - uterine growth retardation, which can lead to chronic cellular immune deficiency and long-term immune system disruption [28].

Zinc lowers the occurrence and time period of acute and chronic diarrhea by 25–30%, and it may also reduce the occurrence of acute lower respiratory infections by 45% (despite Covid-19), and might diminish *Plasmodium falciparum* clinical illness. Zinc was shown to lower malaria prevalence by about 35% in a clinical study in Papua New Guinea [26]. In one study, it was observed that taking Zn supplements before strenuous activity resulted in fewer reactive oxygen species. Driessen et al. (1995) discovered that zinc supplementation increased interleukin (IL)-1 levels in lipopolysaccharide-stimulated peripheral blood mononuclear cell cultures by 50%, Driessen et al. (1995) discovered that zinc supplementation increased interleukin (IL)-1 levels in lipopolysaccharide-stimulated peripheral blood mononuclear cell cultures by 50%. He also discovered that supplementation improved interferon-gamma (INF-γ) secretion about 10 times. Monocyte activation by superantigens, on the other hand, was reduced after supplementation [29].

A high zinc consumption has been related to reduced lymphocyte proliferation, as well as decreased chemotaxis and phagocytosis of circulating polymorphonuclear leukocytes. Additionally, excessive zinc intake can cause anemia, growth retardation, copper shortage, and immunosuppression [28]. Many microorganisms, including yeast, *Plasmodium falciparum*, and HIV, need zinc to replicate and function properly; thus, excess zinc in plasma promotes the growth of those organisms. As a result, both abundant and deficient Zn concentrations have a detrimental influence on the immune system, although the advantages of zinc availability are considerably higher for the host immune system [26].

Many enzymes involved in nucleic acid synthesis, including as DNA polymerase, thymidine kinase, and DNA dependent RNA polymerase, require zinc, which explains zinc's role in lymphoid cell proliferation. Furthermore, zinc is required for the production of some immunological mediators, such as the nonapeptidic hormone thymulin. This peptide promotes T lymphocyte maturation, cytotoxicity, and IL-2 production. Zinc deficiency is also considered to affect cytokine activity because it interferes with the synthesis or action of IL-1, IL-2, IL-3, IL-4, IL-6, IFN-, and TNF-. Zinc deficiency inhibits TH1 cell cytokine production, resulting in an imbalance between TH1 and TH2 cells. Zinc is also considered to influence membrane integrity at the cytoskeletal level and to be a critical intracellular regulator of lymphocyte death *in vitro* and *in vivo* [28].

Covid-19 is being treated with a medication cocktail that includes nitazoxanide, ribavirin, and ivermectin. Nitazoxanide is an antiparasitic medication with antiviral action as well as immune-modulatory properties by inhibiting proinflammatory cytokines such as interleukin-6 and tumor necrosis factor. In vitro investigations showed that nitazoxanide reduced SARSCOV2 replication, but its clinical usefulness has to be investigated further. Ribavirin is a guanosine analogue that has wide antiviral action against both RNA and DNA viruses. They are capable of limiting viral replication and lowering viral burden. Previous clinical trials have

demonstrated that the drug is effective against coronaviruses, and the Chinese government recommends it for SARSCOV2 pneumonia. Ivermectin is indeed a broad-spectrum antiparasitic agent that also has antibacterial and antiviral properties. According to a recent study, Ivermectin reduced SARSCOV2 replication in vitro, making the medication a potential option for SARSCOV2 treatment [30].

In a clinical trial at Mansoura University Hospital, it was observed that dived doses of this combination therapy along with zinc supplements were able to have a cumulative viral clearance rate of 88.7% by the end of 15th day. In the same trial, another group of patients with similar conditions (age, gender, accommodation, and CT lung findings) were given symptomatic care that included paracetamol tablets three times per day, zinc supplements twice day, proper diet and hydration, and azithromycin tablets once each instance are all recommended. It was observed that by the 15th day they had a cumulative viral clearance rate of 13.7% [30].

Zinc's antiviral effects are primarily achieved through physical mechanisms such as virus binding, infection, and uncoating, as well as enzymatic suppression of viral protease and polymerase. Zinc, as seen in mammals, may also be needed for proper folding and action of a variety of viral proteins. Zinc can interfere with viral proteolytic processing by misfolding, direct actions on protease, and tertiary structure modifications. At low endosomal pH, zinc can also efficiently inhibit virus membrane fusion by binding to a specific histidine residue exposed on the viral E1 protein. In cell culture tests, it was shown that high Zn concentrations combined with pyrithione increase cellular import of Zn2+, inhibiting the reproduction of several RNA viruses. Because it is virus-specific, viral RNA-dependent RNA polymerase (RdRp) is an excellent candidate for new antiviral medicines. In instances of rhinoviruses, HCV, and influenza virus, Zn has been found to decrease the role of viral RdRp. Zn2+ is likely to impede

both the correct proteolytic processing of replicase polyproteins and the synthesis of RdRp in coronaviruses [31].

Zinc has a range of antiviral properties and can also boost both the intrinsic and acquired immunity systems. Zinc has been shown to be effective, either directly or indirectly, against a variety of virus types, including nidoviruses, the class of which coronaviruses belong. Zinc deficiency has also been linked to a higher vulnerability to infections in the host. As a result, zinc might be helpful in treating Covid-19.

Selenium

Selenium, as the only trace material to be present in genetic code, is an unique form of trace mineral [32]. The connection with selenoprotiens is what makes selenium an essential trace mineral, 25 genes that code for selenoproteins (selenium-containing proteins) have been detected in the human genome. Selenoproteins serves a number of cellular roles [33]. It is a part of glutathione peroxidase which acts as an antioxidant in extracellular spaces affiliated

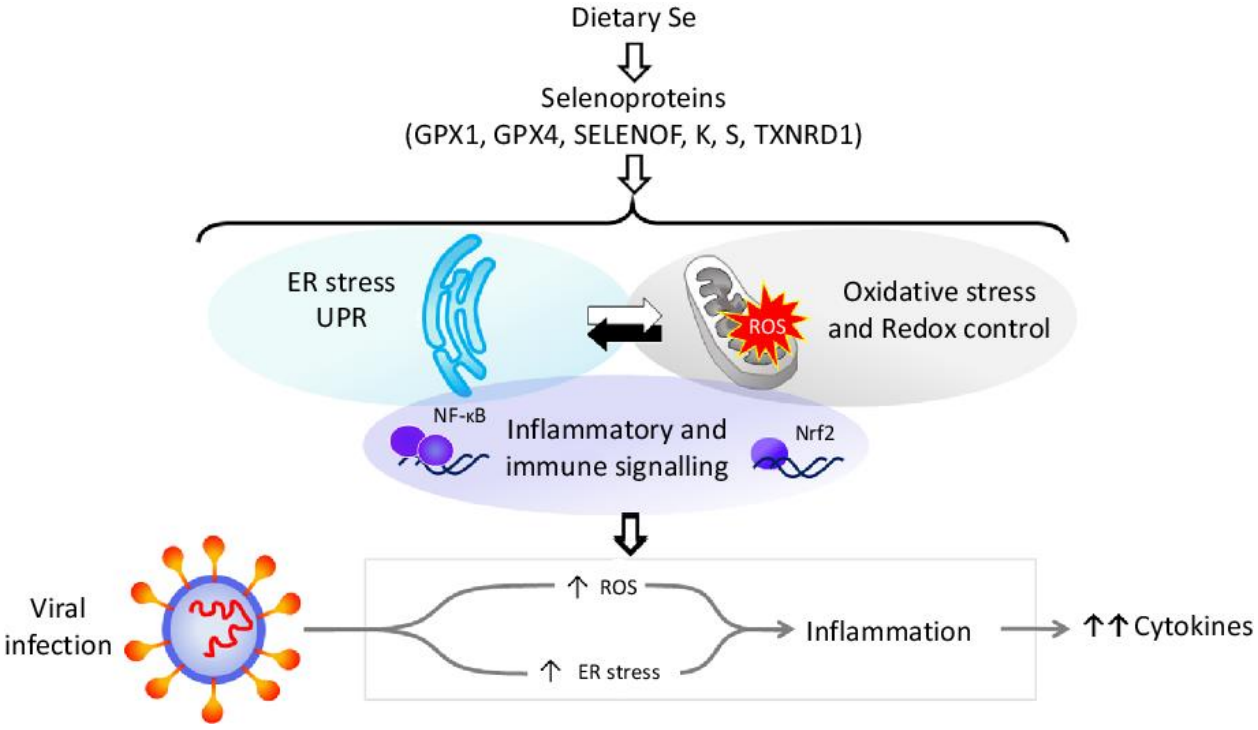

Figure 13: Selenium and the immune response to virus infection. [37]

with cell membranes, particularly the gastrointestinal tract. Other selenoproteins play various roles in cell metabolism [34].

Selenium's antioxidant properties are significant in the removal of hydrogen peroxide and organic hydroperoxides. Deficiency in Se can produce oxidative stress, or an excess of free radicals and other oxidants, in the host, which can cause irreversible damage to the host DNA, compromise cell membrane integrity, alter residues of amino acid at proteins' metal-binding locations [29]. Oxidative stress can also impair development and have an impact on reproduction. However, reactive free oxygen radicals are required by the host for activities such as energy generation, phagocytosis, cell growth control, intercellular communication, and the creation of important biological molecules [35].

Selenium has also shown to act directly against various viruses such as influenza, herpes simplex virus type 1 (HSV-1), hepatitis C virus (HCV), coxsackie virus, and human immunodeficiency virus (HIV) [36]. Keshan disease, an endemic cardiomyopathy, has been attributed to CVB virus infection along with selenium deficiency. It was also observed that adding Selenium containing fertilizer, along direct food supplementation, led to a substantial decrease in occurrence of the acute type of the disease [29]. According to two studies, HIV-infected -patients with suboptimal selenium level have less CD4 T cells and have a greater risk of disease development and death. The incidence of haemorrhagic fever with renal syndrome which is caused by RNA hantaviruses is approximately 6 times greater in regions with Selenium deficiency [37].

Many in vitro experiments with different viral pathogens were conducted after it was discovered that selenium had a direct effect on various viral diseases. In one such study, it was revealed that Se supplementation significantly decreases viral copy quantity in hantavirus-infected human umbilical vein endothelial cells (HUVEC). Another study discovered that

supplementing with selenium decreased viral-induced cell death caused by the West Nile virus. Furthermore, in an *in vitro* research on the epithelial cells of the bronchus, it was found that Selenium supplementation decreased the incidence of cell apoptosis prior to influenza infection. Se supplementation enhanced the pace of removing the virus from the body and decreased the mutation rate of the viral genome of the attenuated polio virus, according to a study done in the United Kingdom. Furthermore, selenium administration increased the cellular antiviral response, which improved the host's response to a viral infection [37].

Se combat viral infections by limiting ROS, ER stress, and blocking a variety of inflammatory pathways. Selenium aids in the recovery of Thioredoxin Reductase (TrxR) biosynthesis in host cells. The TrxR enzyme is a key player in DNA replication, protection against oxidative damage caused by oxygen metabolism, and redox signaling. TrxR knockdown is also used by numerous RNA viruses to attack. Se has also been shown to inhibit virus-induced cell apoptosis, protects endothelial cells and inhibits platelet aggregation in the blood. Furthermore, it is now well known that Se deficiency is linked to increased vulnerability to viral RNA infections and a worse outcome [38].

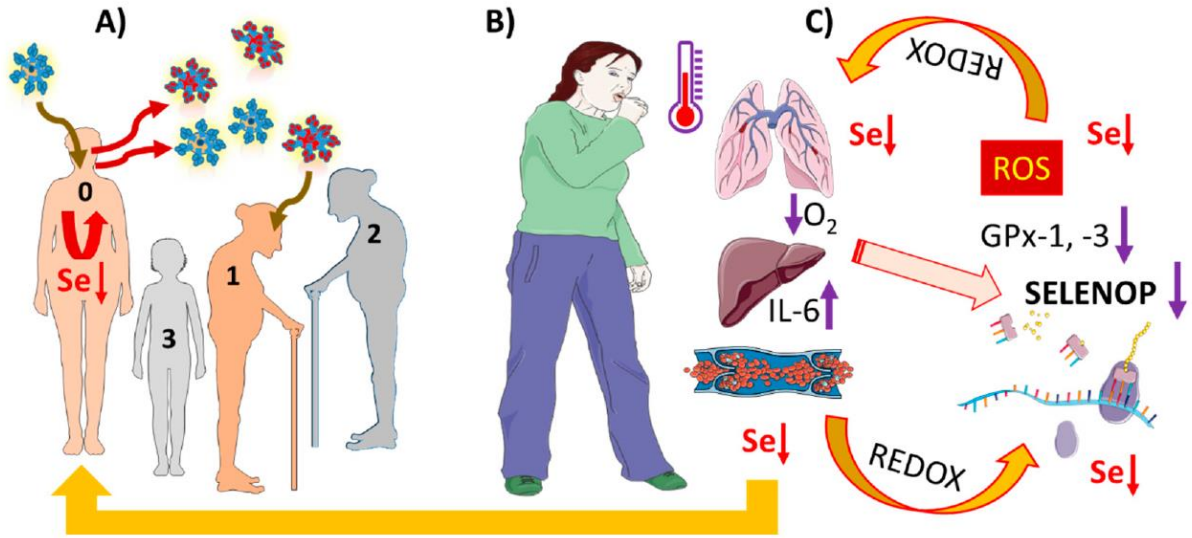

Figure 14: Pathophysiological pathways that may be responsible for poor Se status in severe COVID-19. [39]

It has been shown that the risk of death from acute diseases such as sepsis or polytrauma is inversely proportional to Se status. Research was carried out with the premise that Covid -19 mortality was also inversely proportional to the host's selenium status. The study found that Se status less than the reference population's 2.5th percentile, i.e., [Se] 45.7 g/L and [SELENOP] 2.56 mg/L, are found in 43.4 % and 39.2 % of COVID samples, respectively. Selenium level was somewhat greater in COVID survivors' samples than in non-survivors' samples. Selenium levels in these non-survivors has been recovered through time future survivors, but remaining low or even declining in non-survivors [39]. Another study conducted in south India found that patients had significantly reduced selenium levels of 69.2±8.7ng/mL than controls who had 79.1±10.9ng/mL. There was a statistically important difference (P = 0.0003). Intriguingly, the test sample had a borderline amount of selenium, indicating that the population surveyed may not have an optimal level of this micronutrient [40]. Covid infection spreads independent of Se level. But from the figure, we observe that **(A)** Due to low expression of protective selenoenzymes, some individuals who also have a weak immune system and a low Selenium level (0) can efficiently disseminate the virus (blue) and enable replication of the virus along with speedy evolution of specific harmful virus (red). Subjects with a higher Selenium level (1–3) could be less likely to develop a major disease trajectory. **(B)** SARS-CoV-2 is distinguished by elevated cytokine levels (e.g., IL-6), hypoxia, and inflammation. The mixture of hypoxia and IL-6 suppresses the release of selenoproteins. **(C)** Biosynthesis of Selenium transporters in liver cells, SELENOP is particularly susceptible, leads to a decreased Selenium levels throughout the whole body and insufficient expression of defensive selenoenzymes such as cytosolic GPx1 and plasma GPx3. Inadequate peroxide deactivation as a precursor of reactive oxygen species (ROS) disrupts redox balance, closing a vicious loop in terms of selenoprotein expression, Selenium concentrations, and COVID-19 development. It

is expected that supplementing Se will interrupt this sequence of unfavorable effects and increase the likelihood of recovery [39].

Copper

Copper is an integral micronutrient that has been used by humans since the earliest times. Ancient people used copper to treat various skin problems, purify water, and cure wounds.

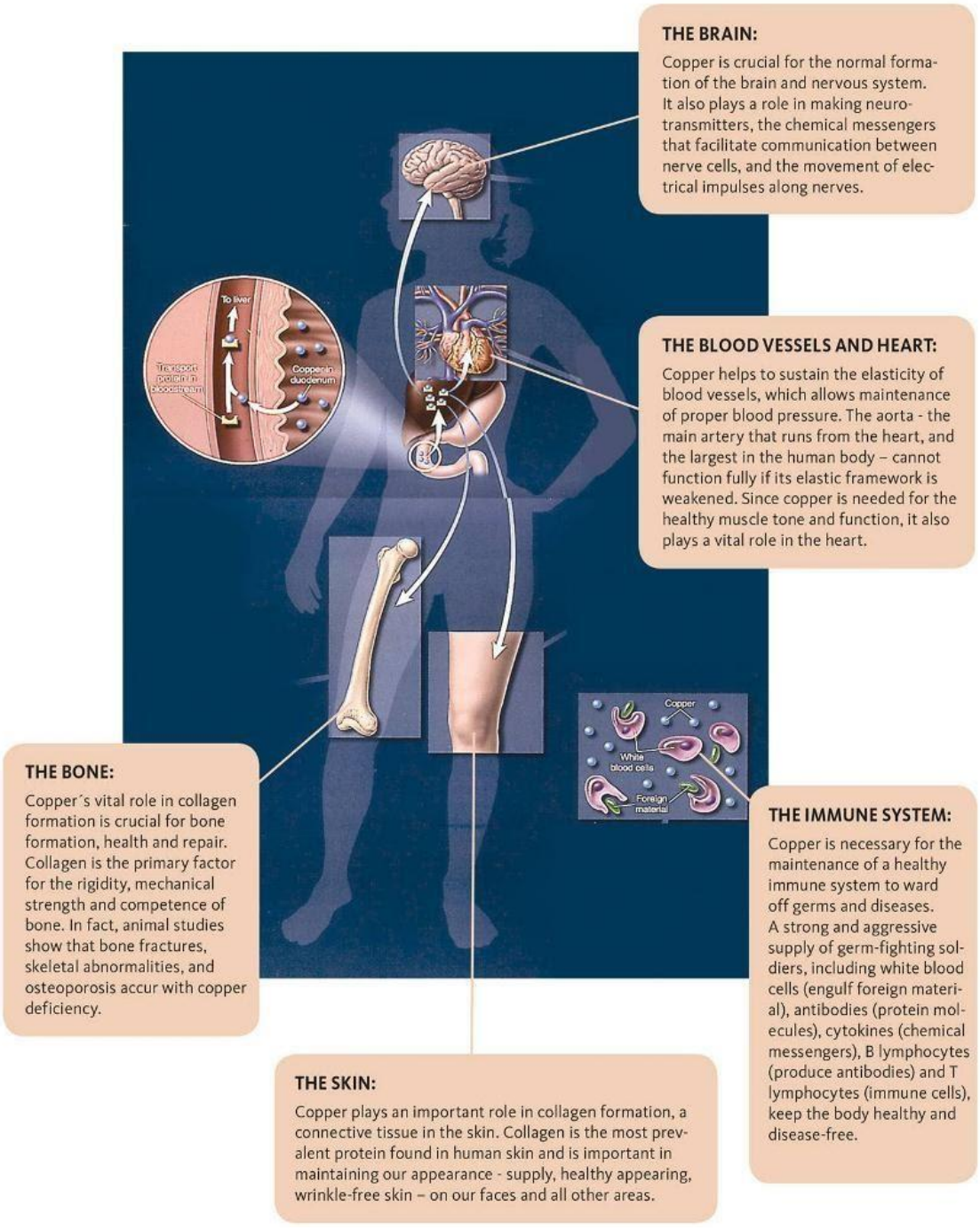

Figure 15: Functions of copper in different parts human body [84]

Professor Bill Keevil, a microbiology professor at Southampton University, demonstrated copper's antimicrobial properties against a number of microorganisms [41]. The specific mechanism by which copper aids in immune system development is unclear. Nevertheless, the immune system is inhibited to various extents depending on the degree of deficiency [42]. Copper deficiency is uncommon, although it can be caused by an excess of zinc. Zinc and copper are antagonistic, since metallothionein (MT), a nonenzymatic protein containing copper, influences the metabolism of trace elements including zinc. A lack of zinc can be to an increase in copper levels, and vice versa. Thus, a healthy balance should be maintained between them [29]; [43].

In reduction-oxidation reactions, it acts as an enzyme activator. Copper also contributes to the production of reactive oxygen species (ROS), which induce oxidative stress and cytotoxicity by interfering with polyunsaturated fatty acid residues in cell membranes, thiol-containing proteins, and nucleic acids [44]. It is also necessary for the proper function of leukocytes, SOD (superoxide dismutase, which reduces reactive oxygen metabolites), and the synthesis of heme [43].

Latest research has shown that copper deficiency decreases interleukin 2 levels in the body, resulting in decreased T-cell proliferation. Even a minor deficiency reduces proliferative response and interleukin concentrations. In extreme copper deficiency, neutrophils are decreased. In both cases, copper deficiency decreases the ability to produce superoxide anion and eliminate ingested microorganisms [42]. Copper's antiviral action is primarily mediated by three mechanisms:

(A) Virus membranes and "envelopes" are destroyed, and the virus's DNA or RNA can be destroyed.

(B) produces reactive oxygen species (ROS) capable of killing the virus

(C) interacts with proteins that are essential to the virus's activity

Cu deficiency signs in humans include white blood cell and bone defects, which can lead to anemia, as well as abnormalities in connective tissue and immune reactions. Insufficient Cu has the most negative effects on immunological function. in children and the geriatric. People that are deficient in copper are more vulnerable to infection. Cu shortage and excess can cause abnormal cellular activity or harm owing to its role in host-pathogen interaction. Throughout infection, macrophages might target Cu-rich invading microorganisms. Infectious illnesses can induce minor alterations in Cu homeostasis, resulting in toxic Cu buildup and pathogen killing. Cu deficiency in the diet has an effect on both innate and adaptive immunity ([45]; [42]; [46])

N-acetylcysteine (NAC) is an amino acid precursor to L-cysteine. This functions as a direct ROS scavenger to control redox state, modulates inflammatory responses, and has indirect antioxidant actions. Furthermore, a study found that NAC reduces airway inflammation and reactivity in asthma patients Copper, in conjunction with NAC, should be used to reduce copper's redox characteristics and limit cellular injury in the treatment of viral infections [47].

Nitric oxide (NO) is a signaling molecule that, when breathed, causes pulmonary vasodilation. It contributes to the catalysis of L-arginine to L-citrulline. NO produced during virus infection may either inhibit or stimulate viral infection. NO suppresses SARS-CoV-2 replication by two mechanisms: an effect on viral RNA production early in the replication cycle and a reduction in palmitoylation of the S protein at the conclusion of the replication cycle, making it effective in the early stages [47].

Copper can improve the human body's response to inflammation by raise ceruloplasmin levels. Ceruloplasmin has indeed been reported to regulate high ferritin levels and to participate in the body's defense. Furthermore, copper can induce autophagy and apoptosis, thus preserving cell antiviral defense. It is being hypothesized that NAC improves immunological reaction by

boosting MnSOD function, high MnSOD levels trigers RNA cleavage. During the early stages of COVID-19 disease, remdesivir (RDV), copper, & NO can all function synergistically to reduce RNA replication. Copper's anti-viral activity is also linked to the oxidation of viral capsid protein by ROS. NAC is speculated to prevent oxidative damage caused by copper in host cells [47].

Copper can be beneficial not only in living beings but also in inanimate objects in the battle against Covid-19. SARS-CoV-2 spreads through droplets and aerosols, and these droplets and aerosols adhere to the surfaces of different inanimate objects. Cleaning with disinfectants is the best way to sterilize these surfaces, but certain surfaces will also have residuals that may infect another human. As a consequence, for high-use surfaces, materials with inherent antimicrobial properties, such as copper, can be much more effective than regular cleansing. New research at the University of Southampton discovered that copper could theoretically inactivate SARS-CoV-2 in less one minute [48]. Copper is thought to oxidize the lipids in the virus envelop, rendering the virus inactive. In an experiment performed at a nursing home for the elderly, it was discovered that placing multiple copper doorknobs greatly decreased infection spread. In a study in which stainless steel was cold sprayed with copper, the anti-viral activity test showed 96% of viruses were inhibited within 2-hours, that was significantly faster than stainless steel.

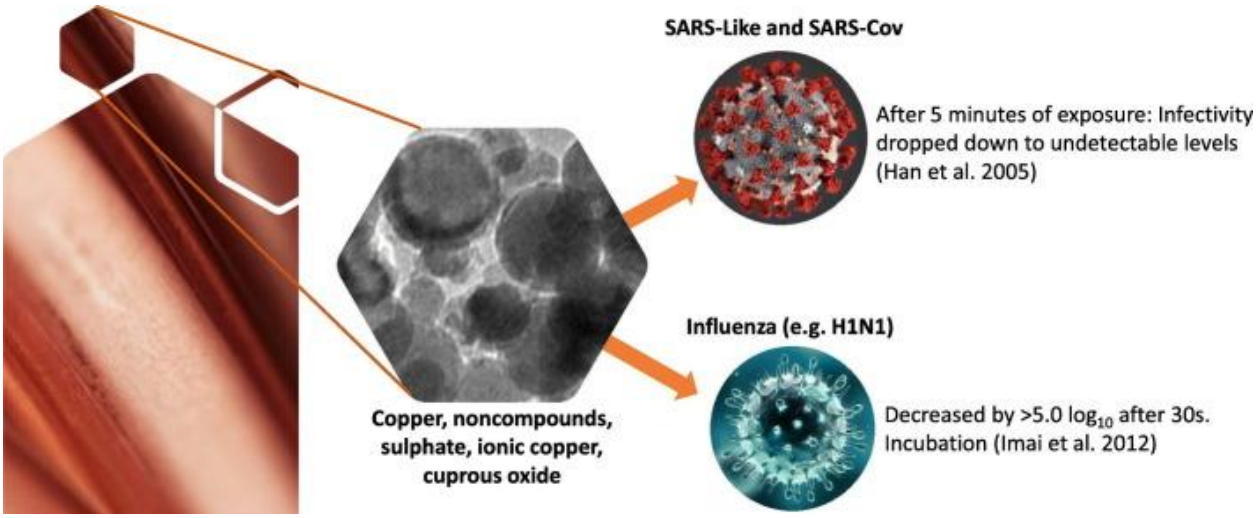

Figure 16: Use of copper in prevention of SARS-coronavirus and influenza viruses [49]

Furthermore, it was discovered that copper-coated samples greatly shorten the COVID-19 virus's lifespan to less than 5 hours. Copper chelates were found to suppress virus release during apoptosis in another study. In addition, copper chlorophyllin has been found to prevent virus-to-cell adhesion on the cell surface in a variety of microorganisms. Furthermore, copper alloys have the ability to change the viral DNA and shape indefinitely. ([49]; [50]; [51]; [52]; [53]).

As a result, copper has been utilized in therapeutic settings to augment standard procedures in order to mitigate risk infection. Furthermore, incorporating copper nanoparticles into polymer/plastic matrix will provide very efficient antibacterial compounds. Copper oxide or nanocompounds can be utilized as filters, face masks, clothing, and hospital common-use devices to lessen viral and bacterial incubation [54]. The Integrated Nanosystems Development Institute at Indiana University Purdue University Indianapolis are developing methods to incorporate copper oxide nanoparticles into facemasks, which will provide a kill layer even if droplets migrate from one side of the mask to the other, with the accompanying possibility of contamination. The copper would destroy the virus en route [55].

Iron

Iron is the most prevalent trace mineral in the human body, and may be found in every cells. In biological systems, the metal has a remarkable capacity to participate in electron transport processes. Bacteria require free iron for growth and development, but it is not easily available in the body; rather, iron occurs in several forms such as ferritin, hemosiderin, myoglobin, hemoglobin, transferrin, and lactoferrin ([56]; [57]; [58]). Iron deficiency, unlike the deficiency of other trace elements, does not enhance the likelihood of infection, rather it decreases infection incidence, as microorganisms rely on host iron for their replication. Infection is frequently associated with iron overload in the host. Iron metabolism in the host is regulated by iron absorption in the stomach, storage in the liver and spleen, blood

transportation, utilization (primarily for erythropoiesis), and recycling by macrophages. But at the other hand, iron excretion is poorly regulated ([59]; [60]).

Hyper-ferritinemia, or a surplus of free iron ions in human body, can also be the reason for a heightened inflammatory state in covid patients. Hemoglobin and neutrophil count were also found to be significantly lower in the patients. It appears that the virus degrades hemoglobin by targeting the heme and dissociating iron to generate porphyrins for cellular proliferation ([61]; [62]). The increased free iron ion concentration in the body produces reactive oxygen species, that induces oxidative stress and lung damage, resulting in lung fibrosis and a reduction in lung function [63]. Since it is widely acknowledged that iron overload promotes viral replication and enhances infection severity, several approaches such as iron chelators, ferroptosis inhibitors, hepcidin modulators, and erythropoietin are being employed in covid therapy with promising results [62].

Iron-chelating agents, such as deferoxamine, deferiprone, and bleomycin, when coupled with antiviral medications inhibit the virus replication cycle in viruses such as HIV-1, CMV, hepatitis B virus (HBV), etc. They might be used as a supplement therapy for Covid-19 patients to help them recover from the illness ([64]; [65]).

Iron Oxides Nanoparticles (IONPs) exhibit antiviral action against Dengue virus, influenza virus (H1N1), and rotavirus, and might potentially be utilized to treat Covid patients. They neutralize viruses by interacting with their surface proteins and interfering with virus attachment and/or entrance into the host cell. A study discovered that IONPs might possibly be employed for antiviral treatment, infection prevention, and infection control. They might also be incorporated into various materials for the production of personal protective equipment (PPE), aprons, masks, gloves, head covering, overshoes, and hospital bed linens, pillow coverings, and curtains [66].

Discussion

Since the breakout of covid-19, human civilization has been thrown into disarray on a global scale, both socially and psychologically. Many people have lost loved ones, and many have lost their livelihoods. Every country faced several serious issues as a result of the pandemic. Since WHO declared covid as a pandemic, society has been looking for several ways to counter covid. All governments have quarantined their populations in order to avoid the virus from spreading, which in itself lessens the burden on medical resources. Because quarantine typically linked with disruptions in work routines, this could often lead to boredom. Furthermore, hearing or reading about the pandemic continually during quarantine might also be stressful. Boredom and stress are also typical causes of eating disorders, such as bingeing, which leads to an increase in carbohydrate, fat, and proteinic food consumption ([67]; [68]). Obesity may develop as a result, elevating the risk of a variety of heart and lung problems as well as serious repercussions for covid-19 [69]. Furthermore, it frequently results in micronutrient deficiency, which further weakens the immune system and makes the body more prone to viral infections [70]. Numerous studies have shown that a lack of minerals in the body leads the thymus to be underdeveloped, resulting in a poor immune system. A balanced diet with adequate macro and micro nutrients is one of the most fundamental ways of enhancing the host immune system and thus battle covid.

Conclusion

This paper attempts to offer a quick description of the SARs-COV-2 illness profile as well as approaches to battle the virus utilizing several minerals. In addition, the effect of minerals on the human immune system was examined. It is obvious that mineral shortage can severely impair the host immune system, resulting in an increased vulnerability to viral infections. On the other side, an overabundance of minerals in the body can also compromise the host's immune system. Moreover, several minerals, in conjunction with the host, aid in the development of viruses in the body. Thus, people should not take supplements without consulting a doctor, and they should eat a well-balanced, immuno-supportive nutritious diet. This review further attempted to shed light on several minerals that are being tested with direct therapy, either in combination or independently. Some minerals, such as cooper, have demonstrated their capacity to kill viruses when kept in direct contact; as a result, researchers are recommending the usage of these minerals on frequently used surfaces, and several scientists recommended the use of nanotechnology in the production of garments containing these materials. To summarize, COVID 19 has a significant impact on society, where correct use of minerals as medicine, an immuno-supportive nutritious food, and sanitization would be beneficial.

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