International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

The Role of Vitamin C Oxidation in Human Health: Mechanisms, Influencing Factors, and Implications in Context of COVID-19

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Abstract: ***Vitamin C, also known as ascorbic acid, is a vital antioxidant in the human body, participating in numerous metabolic processes. However, under specific conditions, vitamin C can undergo oxidation, which may diminish its antioxidant activity and potentially lead to adverse health effects. This paper provides a comprehensive overview of the mechanisms involved in vitamin C oxidation, the factors influencing this process and the potential health implications. The discussion extends to the role of vitamin C in the context of the COVID-19 pandemic, highlighting its potential therapeutic applications. The paper underscores the importance of understanding the oxidation process of vitamin C to preserve its health benefits and nutritional value. Further research is necessary to develop effective strategies for preventing vitamin C oxidation in various mediums, including food, supplements, and pharmaceuticals.***

Keywords: Vitamin C, ascorbic acid, oxidation, antioxidant capacity, reactive oxygen species, enzymatic oxidation, non-enzymatic oxidation, environmental factors, metal ions, temperature, UV radiation, implications, antioxidant, degradation products, bioavailability, preservation techniques, human health.

1. Introduction

Middle of 2019, a worldwide epidemic caused by the coronavirus viral infection known as COVID-19 has been unfolding. By the end of 2022, COVID-19 has already claimed the lives of over six million individuals around the planet. The SARS-CoV-2 coronavirus is responsible for this pandemic because it binds to the host cell surface receptor angiotensin-converting enzyme 2 (ACE2) (1). Rapid injury to the lungs progression with acute respiratory distress syndrome (ARDS) and subsequent multiple organ loss from cytokine storm, a state of uncontrolled systemically hyperinflammation caused by a high level of cytokines, characterizes a critical presentation of COVID-19. More than ninety per cent of COVID-19 related deaths in intensive care units can be attributed to a lack of oxygen, a condition known as acute hypoxemic respiratory failure (AHRF). As many as 15% of those hospitalized developed AHRF due to exposure to COVID-19. Invasive mechanical breathing or ECMO (extracorporeal membrane oxygenation) is necessary for these severely ill individuals with COVID-19 (2).

In particular, the global epidemic has promoted ongoing changes in SARS-CoV-2's spike (S) gene, which has resulted in an increase in genetic diversity at a developmental rate of 0.0004 to 0.002 mutations per nucleotide per year. From Alpha to Omicron, the WHO has used the Greek alphabet to name the VOCs (variants of concern). Until lately patients with mild to severe COVID-19 were treated with a range of medications (3).

Millions of individuals were vaccinated with several vaccinations to try to stop the spread of the disease (4). Unfortunately, there aren't many targeted treatments or vaccinations for emerging strains yet. Patients with severe types of COVID-19 often receive treatment with the antiviral medication remdesivir and dexamethasone (a systemic steroid). Regrettably, there is minimal impact on death, length of hospital stays, or requirement for ventilatory support with the currently accessible antiviral medicines. The symptoms of COVID-19 are similar to those of the common cold. The illness may be resistant to a single pharmacological or chemical treatment. Treatment with high doses of intravenous vitamin C (HDIVC) has been shown to reduce hospitalization, intensive care unit (ICU), and death (5).

Smoking cigarettes has been recognized as an additional determinant contributing to an individual's susceptibility to contracting COVID- 19. When considering the consequences of respiratory infectious diseases, it is frequently observed that cigarette smoking is commonly linked to unfavorable outcomes. In the year 2020, the World Health Organization (WHO) and the Food and Drug Administration (FDA) released official declarations cautioning that the act of smoking could potentially elevate the susceptibility to and severity of COVID-19. Nevertheless, the prevalence of SARS-CoV-2 infection among those who engaged in smoking was found to be rather low. The phenomenon commonly referred to as the "smokers' paradox" aptly characterizes this particular scenario (6).

Vitamin C therapy is being studied for a number of illnesses, notably SARS (severe acute respiratory syndrome), which is due to SARS-CoV, and has been proven for years to be a safe supplementary therapy (7). The therapeutic outcomes of HDIVC therapy are controversial, having a long history of research into the topic. In this article, we discuss the role that ascorbate plays in the generation of nitric oxide (NO), which may help alleviate the effects of COVID-19 and protect against SARS-CoV-2 infection. Possible therapeutic roles of NO, nitrate, nitrite, vitamin C, and vitamin P are reviewed in light of their pleiotropic properties that have occasionally led to confusion, including a revisiting of Pauling's vitamin C therapy suggested in the 1970s.

Individuals with COVID-19 do not receive treatment. It has been determined that hospitalized individuals can safely get treatment with inhaled nitric oxide gas (iNO). The human cardiovascular system and immunity both benefit from NO's pathophysiology involvement (8, 9).

iNO Therapy

Treatments for newborn high blood pressure with the iNO were initially approved by the United States Food and Drug Administration (FDA) in 1999. Experiments using iNO on individuals suffering from severe acute respiratory syndrome (SARS) were conducted that year. Benefits like lower pulmonary hypertension, better arterial oxygenation, and decreased distribution and volume of respiratory penetrate were observed during studies. Therefore, it was sensible to examine the preventative, beneficial and crisis benefits of iNO for COVID-19. iNO can be used as a treatment against COVID-19 and as a rescue medication to increase arterial oxygenation in the event of ARDS (10) . There is an increased risk of AHRF in pregnant patients. With no adverse effects on either mother or child, a recent cohort trial found that iNO decreased the demand for supplemental oxygen and shortened hospital stays for pregnant patients with COVID-19 pneumonia (11).

Several studies have demonstrated that iNO therapy is related to improved oxygenation parameters in COVID-19 patients, however, they have been no significant discussions on the impact of iNO on the clinical outcomes of COVID-19 patients. Rescue therapy including iNO combined with other medicines, has also been tried in COVID-19 patients with ARDS (3).

Inhaled nitric oxide (iNO) treatment makes use of a NO transport device now on the market to target the pulmonary vasculature specifically. The basic idea behind iNO therapy is to increase regional levels of NO by adding NO gas to the pulmonary vasculature. To date, several medical selections are being explored for improving NO levels within COVID-19 patients beyond breathing in of NO oxygen (11, 12) . These include the use of the NOS materials L-arginine and L-citrulline, as well as NO chemical donors like nitrocellulose, S-nitroso-N-acetylpenicillamine (SNAP), and sodium nitroprusside. (SNP), and 1, 2, 5-oxadiazole-2-oxide (furoxan) (13).

The medication (sildenafil citrate) is an initial treatment for the condition (ED) in men that can be obtained over the counter. Sildenafil, in theory, prevents the buildup of cyclic GMP (cGMP) in tissues through blocking an enzyme called phosphodiesterase-5 (PDE5), that is responsible for breaking down cGMP. Sildenafil is being studied for its medical benefits in COVID-19 patients and has been authorized in multiple nations for therapy of high blood pressure in neonates. The powerful vascular action of NO has been the attention of these clinical studies, as it may lessen the likelihood of breathing difficulties. The Smokers' Conundrum High-risk variables for getting COVID-19 or for poorer outcomes include asthma, cigarette smoking, obesity, diabetes, and chronic heart disease. However, there were few severely asthmatic individuals with COVID-19 at the beginning of the worldwide epidemic (2).

2. Methodology

Pursuant to a previous meta-analysis study, individuals with asthma exhibited a lower susceptibility to SARS-CoV-2 infection in comparison to those without asthma. This research provides supporting evidence for this observation. The potential protective effect against SARS-CoV-2 infection in asthma patients may be attributed, at least partially, to the utilization of inhaled corticosteroids, which is associated with decreased levels of ACE2 (14, 15). It is crucial to consider that eosinophilic airway inflammation results in elevated amounts of nitric oxide (NO) emission among people with asthma compared to those who are healthy. Indeed, the exhaled fraction of nitric oxide (NO), commonly referred to as FENO, has been widely embraced as a non-invasive indicator for assessing the inflammation associated with type 2 asthma. Several nations observed a lower prevalence of asthma patients among individuals infected with COVID-19, indicating a potential protective effect of increased nitric oxide (NO) emissions from the airway against SARS-CoV-2 infection. While it seems that non-allergic asthma (non-type 2) has a higher risk, there was a lower prevalence of COVID-19 among individuals with asthma in those particular nations (16).

While it is not recommended to promote smoking as a preventive measure against COVID-19, exploring the mechanism behind the smokers' paradox could offer insights for potential strategies to prevent SARS-CoV-2 infection. Notwithstanding the fact that smoke is unable to be advocated as an antioxidant against COVID-19 (14) .

a) Mechanisms to prevent COVID 19

There are various mechanisms that can contribute to the injury of tissue infected with SARS-CoV-2. These mechanisms include direct cytotoxic effects of the virus, dysfunction of the endothelial cells mediated by the ACE2 receptor used by the virus to enter host cells, resulting in vascular thrombosis, inflammatory damage caused by an exaggerated immune response to the infection, or mechanisms that are not directly dependent on the virus itself. The mRNA vaccine is formulated by employing messenger RNA (mRNA) to provide cellular instructions for synthesizing the spike protein that is prominently displayed on the outer surface of the COVID-19 virus (17). After the administration of a vaccine, the immune cells initiate the production of spike proteins and subsequently present them on the surfaces of cells (1) .

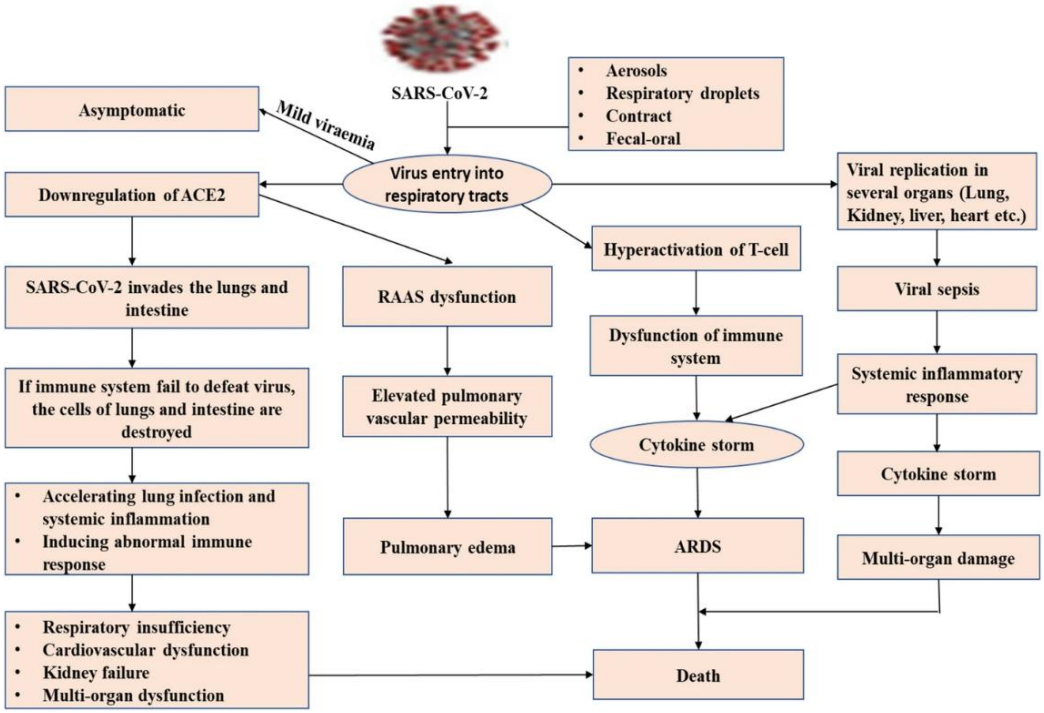

Figure 1: The postulated mechanism by which transmission of SARS-CoV-2 occurs.

SARS-CoV-2, also known as severe acute respiratory syndrome coronavirus 2, ACE2, which stands for angiotensin-converting enzyme 2, ARDS, which refers to acute respiratory distress syndrome, and RAAS, which stands for renin-angiotensin-aldosterone system (18).

b) Implications

The recent KFF/CNN poll indicates that there is a persistent level of apprehension around mental health and substance use, which has endured for three years since the onset of the COVID-19 pandemic. The poll reveals that a substantial majority, approximately 90% of individuals in the United States, perceive the nation to be currently experiencing a mental health crisis. The COVID-19 epidemic has had a multitude of ramifications on the mental health and overall well-being of the general population. These consequences encompass feelings of isolation and loneliness, unemployment and economic instability, as well as physical disease and emotional distress (4).

- The prevalence of anxiety and depression symptoms has shown an upward trend during the pandemic, particularly among persons who have experienced job loss within their households, young adults, and women. Adolescent females have likewise exhibited heightened levels of pessimism and sadness in comparison to their male counterparts.
- The occurrence of drug overdose fatalities exhibited a significant surge among the general populace, aligning with the onset of the pandemic. Moreover, the incidence of such fatalities among adolescents witnessed a notable escalation, surpassing a twofold increase. The mortality rates resulting from drug overdose exhibit the highest prevalence among individuals of American Indian and Alaska Native descent, as well as those of Black ethnicity.

The Indian economy, along to many other regions worldwide, experienced significant economic difficulties as a result of the COVID- 19 pandemic. The Gross Domestic Product (GDP) of India had a contraction of 5.5 percent during the fiscal year 2021 due to the impact of the pandemic. However, it subsequently initiated a recovery phase, with a growth rate of 9.1 percent observed in the fiscal year 2022 (19).

c) Influencing factors

A fast literature study was conducted to identify the parameters that influence the transmission of COVID-19 in close contacts. Subsequently, through the process of creating and evaluating the discovered parameters in two expert panel sessions, a score for the risk of close contact transmission was produced. Additionally, a system for tracing contacts was developed. The transmission and exposure risk of COVID-19 in close contacts is influenced by various factors, such as the mode of disease transmission, features of the infected individual, and environmental conditions. The transmission of viruses can occur through various means, including direct or indirect contact between individuals, the dispersion of coarse or tiny droplets, or contact with contaminated objects. The classification of exposure level for each contact, whether it is categorized as high-risk or low-risk exposure, is contingent upon the corresponding risk of infection. This determination then influences the specific protocols for monitoring and managing those contacts (20).

Hence, it is imperative to thoroughly assess the many elements influencing transmission in contact tracing, and thereafter choose an intervention plan that is commensurate with the evaluation of exposure risk. Moreover, the process of tracing close contacts incurs significant financial expenses and consumes a substantial amount of time, particularly in situations when the disease has reached a high prevalence within the population. Therefore, the establishment of a precise strategy for tracing high-risk relationships will be of utmost significance. The

transmission of COVID-19 in urban areas is influenced by several key parameters, including social distancing practices, geographical location, temperature, humidity, wind speed, economic development level, and race (21).

The quantification of Vitamin C was conducted using high-performance liquid chromatography (HPLC). Methodology: Following the extraction of the blood sample, immediate measures were taken to shield it from any exposure to light, and it was subsequently processed with utmost efficiency. The laboratory sequence is as follows: The plasma (EDTA) was separated through a centrifugation process at 3000 revolutions per minute for 10 minutes at a temperature of 14ºC. Following this, 1 ml of the centrifuged plasma was pipetted into a provided tube containing 1 ml of homocysteine solution (0.7 mg/mL) in 10% trichloroacetic acid. The mixture was thoroughly mixed through repeated agitation. Subsequently, the mixture was subjected to another centrifugation at 3000 revolutions per minute for 10 minutes at a temperature of 14ºC. Finally, the supernatant was separated and immediately frozen at-80ºC before being sent to the central laboratory. The quantification of Vitamin C was accomplished using high-performance liquid chromatography (HPLC) (20).

d) NO generation mechanisms

Hedenstierna et al. postulated that the presence of a brief, concentrated release of nitric oxide (NO) inside cigarette smoke, ranging from around 250 to 1350 ppm per puff, could potentially serve as a preventive measure against SARS-CoV-2 infection. This hypothesis draws a parallel to the rationale provided for the decreased susceptibility of individuals with asthma to contracting COVID-19, as documented in previous studies (22, 23) . Farsalinos et al. postulated that the relatively low incidence of smoking observed among those admitted to hospitals may be attributable to nicotine consumption. The field of study referred to as RNS Biochemistry encompasses the investigation of ribonucleic acid (RNA) molecules and their Besides its significant impact on cardiovascular systems, nitric oxide (NO) also contributes to the immunological and innate components of host defense (11).

Reactive oxygen species (ROS), including superoxide anion (O_2), hydrogen peroxide (H_2O_2), and hypochlorite anion (OCl), are also involved in the mediation of the innate immune response. Phagocytic cells, including neutrophils and activated macrophages, are accountable for the generation of reactive oxygen species (ROS). Because of the non-specific nature of its action, it has the ability to inhibit the growth of a wide variety of pathogens, such as parasites, fungus, bacteria, and viruses. In the same way as reactive oxygen species (ROS) is the word for a group of reactive molecules formed from O_2, reactive molecules coming from NO are referred to as "reactive nitrogen species (RNS) ". The pathophysiological circumstances linked with the main RNS are depicted in Figure 2 (24).

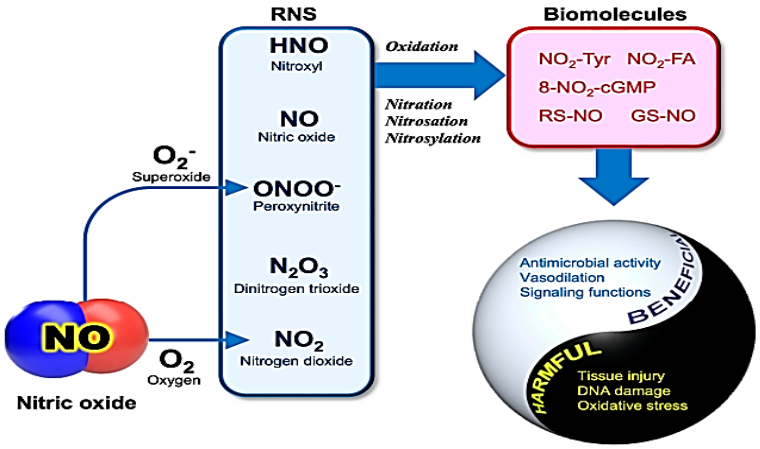

Figure 2: NO and RNS in COVID-19.

The term "reactive nitrogen species" (RNS) is commonly used to refer to NO and other reactive compounds that are produced from NO. In this reaction, NO and O2 create peroxynitrite (ONOO). It is possible that RNS mediate biomolecule oxidation, nitration, nitrosation, and nitrosylation. The results of such reactions can be both helpful and detrimental. Nitro-tyrosine (NO2), 8-nitroguanosine (30, 50)-cyclic monophosphate (cGMP), nitro-fatty acids (NO2), s-nitrosothiol (RS-NO), and S-nitrosoglutathine (GS-NO) are all examples of nitro-acids. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) are highly reactive oxidants linked to oxidative stress in living beings (25) . Most of the chemistry involved in RNS-related reactions is not well known, and it is far more intricate than that of ROS-related reactions, especially under in vivo conditions. Oxidation, nitration (the addition of NO2), nitrosation (the addition of NO+), and nitrosylation (the addition of NO) are all basic reactions involving NO (11).

Nitrative or nitrosative stress, which can damage or kill cells, can result from these reactions if they are allowed to proceed unchecked. Nitration can produce byproducts including nitro-tyrosine (NO2-Tyr), 8-nitroguanosine 30, 50-cyclic monophosphate (8-nitro-cGMP), nitro-fatty acids (NO2-FA), and nitrophenolics from a wide variety of biomolecules. Direct reactions between NO+ and cysteine thiols (RSH) or reduced glutathione (GSH) could generate S-nitrosothiols (RS-NO, GS-NO). Several processes have been postulated for the chemical creation of RS-NO in biological systems, but none have gained widespread acceptance as of yet. In order to inactivate or kill pathogens,

NO uses its specialized RNS processes (nitration, nitrosation, and nitrosylation) to modify biomolecules like enzyme proteins. Keep in mind that inflammation causes damage to host cells as well as the invading cells because these reactions are not selective. It indicates that RNS usage as a defense mechanism against viruses is hazardous for hosts (26).

Peroxynitrite (ONOO), the reaction product between NO and O_2, is a significant interplay between reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can be formed under oxidative stress circumstances where ROS are overproduced, such as during inflammation (27).

When compared to the rate at which O2 is removed by superoxide dismutase (SOD), the rate at which NO and O_2 react is nearly diffusion-regulated (Equation (1)). At pH 12, in the absence of its targets, ONOO is a stable product. Rapid equilibrium between ONOO and its conjugated acid proximations acid (ONOOH, pKa 6.8) (Equation (2)) occurs at physiological pH. ONOOH is a short-lived molecule that spontaneously decays to nitrate (Equation (3)). ONOO is the primary cytotoxic agent in RNS because of its strong reactivity (28) .

$$NO + O_2 \rightarrow ONOO^- \quad (1)$$

$$ONOO + H^+ \rightarrow ONOOH \quad (2)$$

$$ONOOH \rightarrow NO_3^- + H^+ \quad (3)$$

The strong oxidants ONOO and ONOOH may oxidize many different compounds, including thiols, sulfides, ascorbate, and phenols. When combined with bicarbonate anion (HCO3), ONOO can nitrate aromatics chemically in addition to oxidizing molecules. Nitro-tyrosine residues (NO2-Tyr) can lead to the malfunction of proteins or enzymes. Deamination of base pairs by ONOO contributes to DNA fragmentation and RNA virus mutation (29) . The Effects of NO on SARS-CoV-2 Many different viruses, including DNA viruses like murine poxvirus and herpesviruses as well as some RNA viruses, have been shown to be susceptible to NO's antiviral effects. NO's direct antiviral activity prevents viral replication and re-entry into the host cell. Saura et al. (1999) showed that NO-dependent S-matriculation inhibits in vitro reproduction of the RNA virus coxsackievirus by inactivating viral cysteine protease, an enzyme required for replication (30).

It is generally believed that NO's antiviral effect is mediated through S-nitrosylation of viral cysteine-containing enzymes. The culprit that triggered the SARS epidemic was severe acute respiratory syndrome coronavirus (SARS-CoV), a positive-sense RNA virus that is a member of the family Coronaviridae. The replication cycle, protein synthesis, and RNA synthesis of SARS-CoV were all shown to be inhibited in vitro by the NO chemical donor SNAP, which was first discovered in 2005 by Akerstrom et al. Sodium nitroprusside (SNP), another chemical NO donor, did not have this suppressive effect. It has also been observed that SNAP-released NO inhibits SARS-CoV-2 multiplication in Vero E6 cells by targeting the virus's 3CL cysteine protease (29).

Macrophages are multipotent innate immune cells that regulate inflammation and eliminate harmful microbes. S-palmitoylation has emerged as a crucial response for regulatory macrophages during endocytosis, according to recent research. It has been found that NO inhibits ACE2 binding by preventing the palmitoylation of spike (S) proteins. The receptor-binding spike (S) protein of these viruses are originally synthesized in the endoplasmic reticulum (ER) and then undergo significant modifications upon translation in the host Golgi apparatus. The enzyme known as palmitoyl acyltransferase (PAT) located in the Golgi apparatus is accountable for the process of S-palmitoylation. This process involves the attachment of the saturated fat palmitate (C16: 0) to the thiol group (-SH) of cysteine residues found in proteins. The hydrophobicity of proteins is enhanced via modification, a necessary process for facilitating cell-cell union. The process of palmitoylation has the potential to decrease the enzymatic activity of endothelial NO synthase (eNOS), which is a specific isoform responsible for the production of nitric oxide (NO) in the host organism. The potential outcome of diminished intercellular fusion can be attributed to the S-nitrosylation of the spike (S) protein of SARS-CoV, facilitated by nitric oxide (NO), leading to a potential reduction in the palmitoylation of the spike (S) protein. The potential antiviral efficacy of nitric oxide (NO) versus the coronavirus is believed to be mediated by a mechanism that disrupts the cysteine palmitoylation process of the spike (S) protein (15).

The Role of Redox Reactions in NO Production Several different viruses, including SARS-CoV-2, are vulnerable to NO's potent antiviral effects. NOS is crucial to the production of endogenous NO in animals. To be clear, NO is produced endogenously in other ways besides the NOS response. In addition to NOS, several biological pathways also contribute to NO generation. The "nitrate-nitrite-NO pathway", "NOS-independent mechanism", "nitrite-dependent NO production pathway", "nitrite pathway", and "reductive pathway" are all names given to these various pathways. Numerous studies have shown that redox enzymes or reductants can convert inorganic nitrite (NO_2) to NO. The NOS-independent NO generation mechanism (henceforth referred to as the oxidative mechanism) appears to be more well-known and understood (31) . Our current understanding of the numerous NO sources important to the pathophysiology of COVID-19 is summarized in Figure 3.

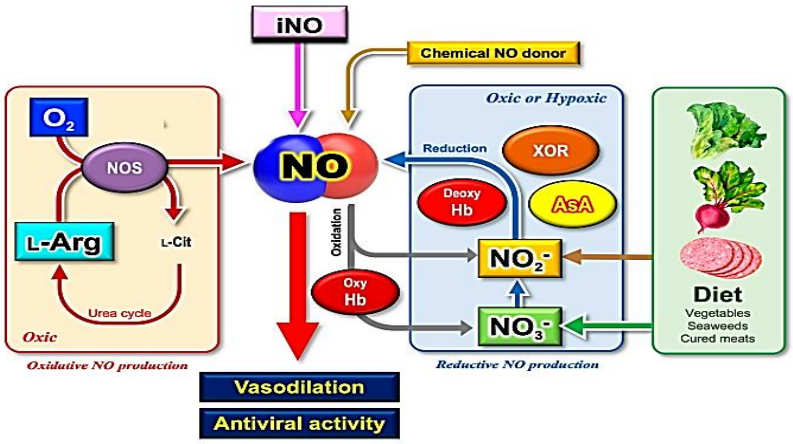

Figure 3: Diversity of NO generation mechanisms (28)

Nitric oxide (NO) plays a crucial role in numerous physiological processes in the human body, particularly in the mechanism of vasodilation. Additionally, there exists a hypothesis suggesting that nitric oxide (NO) may impede viral infection by suppressing the replication of several viruses, including SARS-CoV. This would confer advantages in the battle against SARS-CoV. There exist two distinct approaches for the generation of nitric oxide (NO), commonly known as NOS-dependent and NOS-independent NO-producing systems, respectively. Inorganic nitrate (NO_3) and/or nitrite (NO_2) are generated through the oxidation of nitrogen monoxide (NO) (31, 32) . This phenomenon manifests irrespective of the courses of action pursued. Nitrate (NO3) can be acquired by individuals through their typical dietary intake, which may encompass the consumption of green vegetables or seaweeds. These food items may also enhance the bioavailability of nitric oxide (NO). NO refers to nitric oxide, iNO is an abbreviation for inhaled nitric oxide, NOS stands for nitric oxide synthase, oxy-Hb represents oxyhaemoglobin, deoxy-Hb represents deoxyhemoglobin, XOR stands for xanthine oxidoreductase, NO_2 denotes inorganic nitrite, and NO_3 represents inorganic nitrate (31, 33).

There has been a longstanding discourse on the pharmacological impacts of Vitamin C, spanning several years. While Szent-Gyorgyi's research provided evidence for the role of ascorbate as vitamin C in preventing scurvy (34) , the potential efficacy of ascorbate in combating viral diseases had been hypothesized prior to this discovery. However, the name Linus Pauling is widely recognized for its strong association with vitamin C, surpassing any other contributing component. Based on his own meta-analysis, which was conducted in the early stages of research, and the clinical trial data accessible at the time, Linus Pauling asserted in 1971 that the oral ingestion of vitamin C could potentially reduce the occurrence and severity of the common cold. The formulation of this theory was based on the analysis of data obtained from clinical trials. In 1970, Linus Pauling wrote a book titled "Vitamin C and the Common Cold, " wherein he advocated for the potential efficacy of vitamin C in the treatment of the common cold. One of the multiple factors contributing to the persistent scientific and political debates around the efficacy of vitamin C in treating the common cold and other illnesses since the 1970s is the narrow scope of the clinical trial data utilized by Pauling. Consequently, the aforementioned articles contained conclusions that were unavoidably influenced by prejudice. Even after the passage of fifty years, ongoing and impassioned debates persist over this subject matter, rendering it a perpetual narrative. The utilization of vitamin C as a medicinal agent is largely disapproved by modern medical experts (21, 35).

Pauling noted in an article, "In the search for a drug to combat a disease, the effort is usually made to find one that is 100 percent effective" (36) . He was explaining why medical practitioners are not enthused about the observation that vitamin C reduces the incidence of the common cold by 31%. He went on to say, "Also, there appears to have existed a feeling that the intake of vitamin C should be kept as small as possible, even though it is known that this vitamin has an extremely low potential for toxicity. " It is reasonable to anticipate that pharmaceutical medications, such as antiviral treatments, will have a high efficacy at low concentrations. This is due to the fact that drugs are typically highly harmful at greater concentrations. Because of the potential for adverse consequences, taking a high dose of a medicine can frequently be extremely hazardous and even lethal. Even at doses that are considered to be quite low, there is a possibility of experiencing major adverse consequences. For instance, damage to the liver brought on by medication is a challenge in the treatment of COVID-19. There is also an argument in favour of using vaccines. Vitamin C, on the other hand, possesses almost no harmful effects, even when it is present in the body at saturation levels (20, 37).

3. Discussion

Vitamin C's Pleiotropic Effects Require a Large Dose
Pauling stressed the necessity of keeping up with vitamin C intake to keep one's immune system strong and, for example, to avoid catching a cold. However, the FDA's RDA was significantly lower than the quantities established by Pauling and his predecessors. Pauling wrote that the Recommended Dietary Allowance (in its 1980 edition from the FDA) for adult males was 60 milligrams, but that the recommendations of his predecessors and himself were over a thousand milligrams. The FDA's RDA number was set solely to avoid scurvy, which explains the huge discrepancy among these recommendations (35).

Both Szent-Györgyi and Pauling believed that the recommended daily allowance (RDA) for vitamin C was far too low. Szent-Gyorgyi said, "Scurvy is not the first sign of the deficiency but a premortal syndrome" (38) , in response to a question from Pauling. The widespread belief that vitamin C treats just scurvy has, unfortunately, obscured the many beneficial physiological roles it plays. Recently, a great deal of evidence regarding vitamin C's pleotropic roles outside of scurvy prophylaxis has collected. Due to its wide range of uses and individual differences, Pauling's (1986) recommendation of 1, 000 to 18, 000 milligrams of vitamin C per day is not excessive. Vitamin C RDAs should be tailored to each individual based on their genetic makeup, dietary quality, and health condition.8.1 Refining Pauling's Theory Pauling first used the phrase "molecular disease" after discovering the underlying molecular causes of sickle cell anemia (39).

In 1949, Scientist reported "Sickle cell anemia, a molecular disease, " a landmark article that ushered in the modern era of molecular biology and medicine. Pauling, however, did not devote much time or energy to "molecular medicine, " likely because he was aware of the challenges inherent in developing successful molecular treatments that are grounded in molecular principles. The current pharmacological paradigm suggests that synthetic medications that target pathogenic microorganisms by interacting with the particular molecules of pathogens ought to be developed. Koch's postulates, that originated over a century ago, provide the basis of this paradigm. Since Pauling's vitamin C therapy is based on a paradigm that is completely different from the present theories, this Koch's postulates-based paradigm may make vitamin C less acceptable for medical professionals (2).

Disease, according to "Western" or "modern" medical theory, is any abnormality in the body's normal physiological processes. According to this theory, drugs are thought to affect only one part of a larger physiological mechanism (40) . Molecular medicine refers to this approach of curing illness. These drugs often work by blocking certain enzymes or transporters, illustrating the "one-to-one" correspondence between the medicine and its intended target molecule in the context of the structure-function relationship. If a single factor, like a protein or an enzyme, is thought to be responsible for a disease, the "one-to-one" concept of medicine and pharmacology can be very effective. However, most incurable diseases are actually syndromes, which are influenced by a number of interrelated factors. One such instance is COVID-19 (10, 30) .
Searching back over decades of studies, we can see how public opinion on the effects of basic chemicals like nitrite, nitrate, nitrous oxide, and oxygen has shifted over time. Regarding the physiological roles of those ubiquitous molecules, there have always been conflicting findings and interpretations. The chemical Fenton reaction, in which vitamin C participates, results in the formation of highly hazardous reactive oxygen species (ROS; •OH, hydroxyl radicals) [6, 19]. Supplementing with the glutathione precursor cysteine may prevent oxidative stress conditions brought on by the excessive intake of DHA (the oxidized form of ascorbate) into the cells, in which the reductants GSH and NADPH are depleted for ascorbate regeneration. The two seemingly opposite impacts of those tiny chemicals can leave non-specialists wondering whether or not they are beneficial to human health. Furthermore, the nitrite-NO relationship (Figure 2) is circular, which raises the chicken-and-egg question: which comes first, the substrate or the product? Proteins, carbohydrates, lipids, DNA, and RNA are examples of significant target molecules in biochemistry and molecular biology because they are big, stable, and structurally distinct (41, 42) .

These compounds have the potential to be useful molecular medicine targets. NO and nitrite is fundamentally different from the typical biomolecules in that they are highly reactive, large, complex, and therefore rare. These characteristics make it difficult to use traditional methods to deduce the physiological roles of these ubiquitous compounds. Pauling argues that the "optimal molecular concentrations of biological substances that are normally present in the body, such as vitamin C, are critical for the function of organs" (27) .

Pauling said that the ideal level of focus may be different for each person. More important than a rigid classification of impacts or targets is recognizing the delicate balance between those simple and universal biomolecules, which is essential for comprehending their physiological or pharmacological actions. The physicist Fritjof Capra first pointed out the similarities between Western science and Eastern philosophy in his book The Tao of Physics. The underlying beliefs of traditional Chinese medicine are incompatible with those of "Western" science. Pauling shares the view that understanding the fine balance is the final answer to such Eastern beliefs. Through cysteine thiolpersulfidation (Cys-SSH) and polysulfidation (Cys-RSS (n) H), new research suggests that H_2S/HSalso plays a role in the control of physiological processes. We call these sulfur compounds that are prone to reactions reactive sulfur species (RSS) (38, 43).

In cysteine thiols, the complex chemical interactions between reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS) are particularly evident. Saliva and gastric juice include the sulfur-containing chemical thiocyanate (SCN -), in addition to nitrite and ascorbate (44) . Cruciferous vegetables (Cruciferae or Brassicaceae), such as cabbage, have high concentrations of the H2S chemical donor isothiocyanates, which have been linked to a reduction in numerous ailments. Optimization of the redox balance depends in no little part on RSS. The ideal concentrations of ROS, RNS, and RSS, such as H2O2, NO, and H2S, that are routinely present in the body are crucial for the function of organs, notably in vascular systems and immune systems, according to our revised version of Pauling's theory (13, 58).

4. Conclusions

Similarly occurs throughout inflammatory processes, cells in the host can get damaged by long-term exposure to elevated levels of NO. The latest study by Del Sorbo et al. (2022) suggests that a brief release of NO at high levels (hundreds ppm) ought to produce optimal antiviral properties on COVID-19 while affecting the host's cells. Finally, we

suggest that a chemically caused periodic NO burst, involving nitrite (or nitrate) and vitamin C (or vitamin P, Phytophenolics, and betalains), is a promising therapeutic approach for preventing and mitigating COVID-19. As a result, the reductive NO-generating mechanism merits consideration in the development of clinical treatments and the design of clinical trials, as well as in the interpretation of results from these studies. It is worth noting that the reductive NO production technique is also expected to treat chronic disorders like hypertension that are linked to vascular system malfunction.

Vitamin C's preventive effects in the ongoing COVID-19 pandemic may be due to its ability to strengthen the defenses of the body. Standard neutrophil function, collecting of oxidative organisms, regrowth of vitamin E, shifting of pathways of signaling, stimulation of inflammatory genes, activating of the communication chain reaction, oversight of mediators of inflammation, gene regulation, phagocytosis, and signalling networks in T cells, and increased neutrophil motility to the site of infection are all aided by vitamin C, a potent antioxidant. The avoidance and handling of COVID-19 infection depend critically on these features. Therefore, consistent vitamin C intake is necessary for developing robust defense against COVID-19 infection. Regrettably, we have not yet identified quantitative parameters with which to track the redox equilibrium at the cellular, tissue, organ, and organism levels. Dogs have been shown in recent pilot research to be highly sensitive and specific in distinguishing between the volatile chemicals present in the respiratory secretions of patients with COVID-19 and those of healthy controls. One promising area of personalized healthcare involves the invasive monitoring of someone's inner redox condition through the study of inhaled gasses and/or organic compounds that are volatile.

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