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OPTIMIZATION OF VITAMIN C THERAPY FOR PREVENTION AND MANAGEMENT OF RESPIRATORY INFECTIONS

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ABSTRACT

Vitamin C, is a crucial water-soluble nutrient. In order to maintain a normal plasma level of 50 mol/L, which is the mean plasma level in UK adults, the EU Average Requirement is 90 mg/day for males and 80 mg/day for women. This can be insufficient when a person is exposed to a virus and is experiencing physiological stress, but it is sufficient to prevent scurvy. Everyone should take 200 mg of a supplement, according to a recommendation made by an expert panel working with the Swiss Society of Nutrition, "to address the nutrient gap for the general population and notably for the people age 65 and above." The purpose of this supplement is to boost the immune system. Vitamin C contains strong anti-oxidant and anti-inflammatory properties that lower the risk of tissue damage caused by oxidative stress and diminish the cytokine storm, an overactive inflammatory response. By boosting interferon synthesis and promoting lymphocyte proliferation, vitamin C enhances the host's defence against viral infection. It has been demonstrated that vitamin C can help prevent other respiratory infections like influenza, cold, pneumonia, ARDS, and treat some severe COVID-19 and also anti-microbial effects.

KEYWORDS: Vitamin c, deficiency, influenza, cold, pneumonia, COVID19, antimicrobials, sepsis.

INTRODUCTION

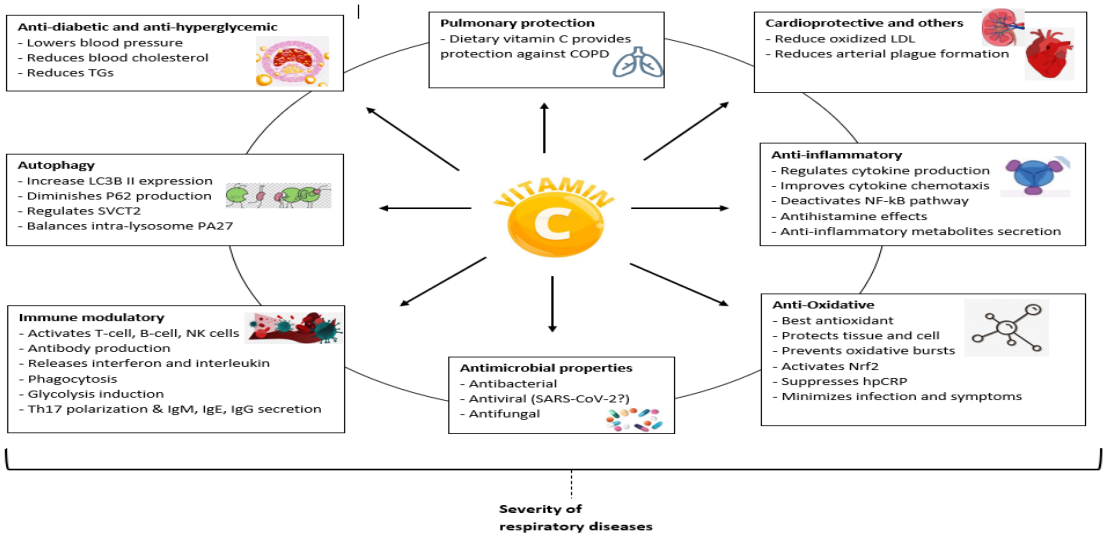
Infectious disorders that affect the respiratory system include respiratory tract infections (RTIs).[1] This type of illness is typically further divided into lower respiratory tract infections

(LRTI) and upper respiratory tract infections (URI or URTI) (LRI or LRTI). The severity of lower respiratory infections like pneumonia typically exceeds that of upper respiratory illnesses like the common cold. Respiratory infections frequently follow distinct seasonal patterns, with the winter months being more problematic in temperate countries. Winter respiratory infection peaks are caused by a variety of reasons, including alterations in human behaviour and environmental variables. Temperature and relative humidity are two environmental factors that have an impact on viruses that cause respiratory illnesses. Winters in temperate regions feature decreased relative humidity, which is believed to accelerate the spread of the flu.[2]

Ascorbic acid, also known as vitamin C, is a crucial water-soluble nutrient. In plants, it is created from fructose, while in practically all mammals, it is created from glucose. Since the final enzyme, gulonolactone oxidase (GULO), essential for ascorbic acid synthesis is lacking due to gene changes that occurred before the emergence of Homo sapiens, it cannot be synthesised by primates, the majority of bats, guinea pigs, and a limited number of birds and fish.[3] As a result, all of these species rely on vitamin C in their diets. Primates require a sufficient supply of food, which ranges from 4.5 g per day for gorillas.[4] to 600 mg per day for smaller monkeys (7.5 kg, or one-tenth the size of an adult human).[5] In order to maintain a normal plasma level of 50 mol/L.[6] which is the mean plasma level in UK adults,[7] the EU Average Requirement is 90 mg/day for males and 80 mg/day for women. This can be insufficient when a person is exposed to a virus and is experiencing physiological stress, but it is sufficient to prevent scurvy. Everyone should take 200 mg of a supplement, according to a recommendation made by an expert panel working with the Swiss Society of Nutrition, "to address the nutrient gap for the general population and notably for the people age 65 and above." The purpose of this supplement is to boost the immune system.[8] For persons over 50, the Linus Pauling Institute advises 400 mg.[9] A daily dose of 200 mg is recommended by pharmacokinetic studies in healthy volunteers to achieve a plasma level between 70 and 90 mol/L.[10,11] The greatest tolerable oral dose, 1 g daily or 3 g every four hours, results in complete plasma saturation, with a predicted peak plasma concentration of around 220 mol/L.[12] Plasma vitamin C levels are increased by around ten times with the same amount administered intravenously. In order to maintain normal plasma levels between 60 and 80 mol/L, higher doses of vitamin C are likely required during viral infections.[13,14] Although it has not yet been shown, increased plasma levels would be in line with the findings of the clinical trials covered in this review.

WHAT CAUSES VITAMIN C DEFICIENCY

Infection, trauma, and surgery are examples of physiological stresses that cause a rapid drop in human plasma vitamin C levels. This phenomenon frequently causes overt vitamin C deficiency in hospitalised patients, which is defined as a plasma level of vitamin C 11 mol/L.[15-20] The vitamin C-deficiency disease scurvy has long been associated with pneumonia which led to the view that vitamin C may influence susceptibility to respiratory infections.[21] In other words, people deficient in vitamin C may be more susceptible to severe respiratory infections such as pneumonia. A prospective study of 19,357 men and women followed over 20 years found that people in the top quartiles of baseline plasma vitamin C concentrations had a 30% lower risk of pneumonia.[22] Furthermore, meta-analysis has indicated a reduction in the risk of pneumonia with oral vitamin C supplementation, particularly in individuals with low dietary intakes.[23]



CLINICAL ROLE OF VITAMIN C IN PNEUMONIA

In the most recent Cochrane review on vitamin C and pneumonia, Padhani et al.[24] In a research article, they make an inaccurate assertion that they were the authors of the prior Cochrane review on vitamin C and pneumonia.[25] Regarding vitamin C and the common cold, we authored the Cochrane review.[26] However, the paper was generally focused in respiratory infections.[24]

"Types of studies: We included randomised controlled trials (RCTs) and quasi-RCTs," Padhani says in the part titled "Criteria for considering studies for this review." Two of the listed trials.[27,28] do not appear to be RCTs or quasi-RCTs, though there is no proof of this.

According to Wahed et al., "the sample procedure was systematic sampling, and every first patient was given the intervention and every second patient from a prepared register was treated as a control".[27,78] There were six active treatment groups: five micronutrients (N = 200), 40 each of the vitamins A, C, and E, 40 each of folic acid and 40 each of zinc. Each of the six active treatment's control groups was combined into a single control group (N = 400) for the analysis. Patients were divided alternately into the vitamin C (N = 40) and control (N = 40) groups based on Wahed's description. However, there is no information available regarding the actual control group (N = 40) for vitamin C. Only the 400-patient pooled control group is displayed. Over the course of the three-year trial, it is unclear if all six therapies were administered simultaneously on the same wards.

Therefore, it cannot be said with certainty that the 40-patient vitamin C group and the 400-patient pooled control group are equivalent. The presented results do not take into account the alternate allocation, notwithstanding the possibility. The Supplementary File goes into further detail on a few additional issues with this trial. This trial ought to have been disregarded by Padhani due to the numerous methodological and reporting flaws.

Khan et al. divided 111 patients into vitamin C and placebo groups, although they don't specify how they did so in their paper.[28] Without proof, it should not be presumed that a trial is an RCT or quasi-RCT. Some trials' allocation strategies led to comparisons that were invalid. One experiment, for instance, gave vitamin C to students one winter and compared their results to those of a separate set of students seen the winter before.[29] It is unclear in the Khan study if the two groups were investigated concurrently on the same wards. The Khan trial should likewise have been disregarded in light of Padhani's inclusion requirements.

We concur with their findings that "additional high-quality studies are needed to investigate the impact of vitamin C supplementation in the prevention and treatment of pneumonia," but that result is not original given that it has been expressed numerous times over the previous decades.[25,30,32]

CLINICAL ROLE OF VITAMIN C IN COVID 19

Numerous treatment plans have been tested since the coronavirus disease 2019 "COVID-19" pandemic began under the auspices of compassionate use. Aside from remdesivir, which showed promising results and received an emergency approval from the Food and Drug Administration (FDA) to be used in the treatment of COVID-19, no specific antiviral medication has been shown to be effective thus far.[33,34] Because of this, supportive therapy, which includes the addition of micronutrients like vitamin C, has emerged as an essential component of COVID-19 care. It has been observed that vitamin C levels in serum and leukocytes decrease during the infection's acute phase.[35,36] High doses of vitamin C supplementation were observed to reduce the severity and duration of respiratory virus infections in prior clinical trials.[37] These results suggest that vitamin C could be used to treat COVID-19 because it might enhance the immune system's defences against the new coronavirus (SARS-CoV-2).

The direct viral virulence effect contributes to some of the pathological damage brought on by SARS-CoV-2 infection, but the main causes are a strong host immunological response and oxidative stress brought on by the generation of free radicals.[37] Adult respiratory distress syndrome (ARDS) develops as a result of the SARS-CoV-2 infection's excessive proinflammatory cytokine release, which causes a cytokine storm, and increased creation of reactive oxygen species, both of which significantly damage the lungs. In particular in patients older than 60 years, ARDS.[38,39] can result in additional worsening and the development of septic shock, both of which are frequent causes of intensive care unit (ICU) admission and mortality.[40,31] There is proof that vitamin C has immunomodulatory effects and is a powerful antioxidant.[42,44]

Pneumonia and vitamin C insufficiency have both been linked.[47] In fact, due to oxidative stress and increased physiological demand, vitamin C body stores are depleted in individuals with acute chest infections.[46] Therefore, vitamin C supplements could be required during the acute stage of infection to restore normal vitamin C levels. An RCT found that giving hospitalised elderly patients with acute respiratory infections, such as acute bronchitis and pneumonia, 200 mg/day of oral vitamin C for four weeks improved the clinical outcome (reduced severity of disease and decreased mortality rate).[47] The more seriously ill patients had the greatest clinical improvement.[47]

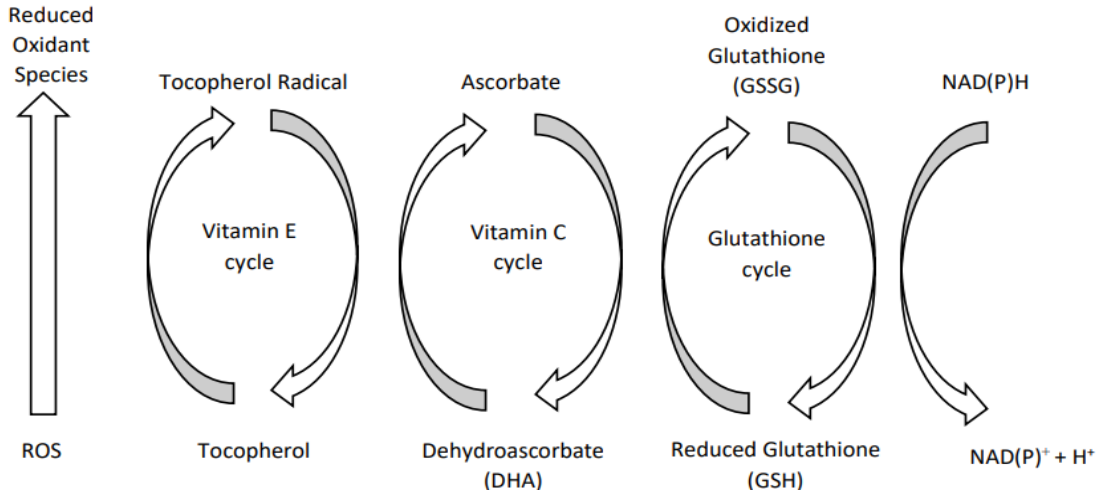
CLINICAL ROLE OF VITAMIN C IN COLD AND INFLUENZA

In the 1970s, vitamin C became widely used after Nobel laureate Linus Pauling determined from randomised controlled trials (RCTs) that it prevented and treated colds.[48,49] Supplementation with more than 200 mg of vitamin C did not lower the prevalence of colds in the general population, according to a Cochrane Review of placebo-controlled trials using oral vitamin C for cold prevention and treatment.[50] However, vitamin C decreased the frequency of colds by 52% (p 0.0001) in five trials including a total of 598 marathon runners, skiers, and soldiers participating in subarctic training.[50] These findings suggest that, under specific circumstances, such as during brief bursts of intense exercise, vitamin C may affect resistance to viral infections. Trials that regularly administered vitamin C reduced the duration of infections in adults by 8% and in children by 14%, with an apparent dose-dependency up to 6-8 g/day.[50,52] In contrast, trials that administered vitamin C only after the onset of symptoms failed to consistently demonstrate benefits. When given regularly, vitamin C can lessen the intensity of colds and can shorten their duration in children by 18% (1 to 2 g/day).[50]

The most recent placebo-controlled research conducted in the UK shows a clinically significant difference in the number, duration, and severity of colds.[51] In this trial, 168 individuals were randomly assigned to receive vitamin C (2 500 mg daily) or a placebo for a 60-day winter period. The vitamin C group had fewer days with virally challenged "colds" (85 vs. 178, p = 0.03), fewer days with severe symptoms (1.8 vs. 3.1 days, p = 0.03), and fewer colds overall (37 vs. 50, p = 0.05). Significantly fewer participants (2/84 on vitamin C vs. 16/84 in the placebo group; p = 0.04) suffered two colds during the experiment.[52]

In conclusion, oral vitamin C has been proven to have a dose-dependent effect on reducing the severity and speeding up the resolution of cold symptoms. The majority of people who have SARS-CoV-2 infection and do not progress into the acute sickness phase share a set of symptoms with individuals who have colds, which are brought on by over 100 distinct virus types, some of which are coronaviruses. Another justification for believing that vitamin C's benefits in lowering severity and duration of illness are not virus-specific is the similarity of symptoms between SARS-CoV-2-related symptoms and the disease-modifying effect of vitamin C across a wide spectrum of cold-related viruses. Reduced cold duration, severity, and frequency are all impacts that may be fairly hypothesised, decrease conversion from the mild infection to the critical phase of COVID-19 in the setting of SARS-CoV-2. Given the

consistent impact of consistent vitamin C consumption on the length and severity of colds, as well as the low cost and safety, it would be desirable to evaluate the therapeutic vitamin C benefits for patients with respiratory viral infections. The above estimates may justify a regular increased daily intake of vitamin C for the period when the virus prevalence is high, when a patient has a virus infection with active cold symptoms, in those testing PCR positive to SARS-CoV-2, and in COVID-19 hospitalised patients; an oral dose of up to 6-8 g/day might be considered. This is because the disease caused by the novel coronavirus can be more severe than ordinary viral infections. The most efficient dose has not yet been established, despite Pauling's prescription that 1 g of oral ascorbic acid be taken every hour while the illness is active.



EFFECTS OF VITAMIN C ON CELL CULTURES

Pharmacological effects of vitamin C on various pathophysiological conditions evaluated using cell culture system:

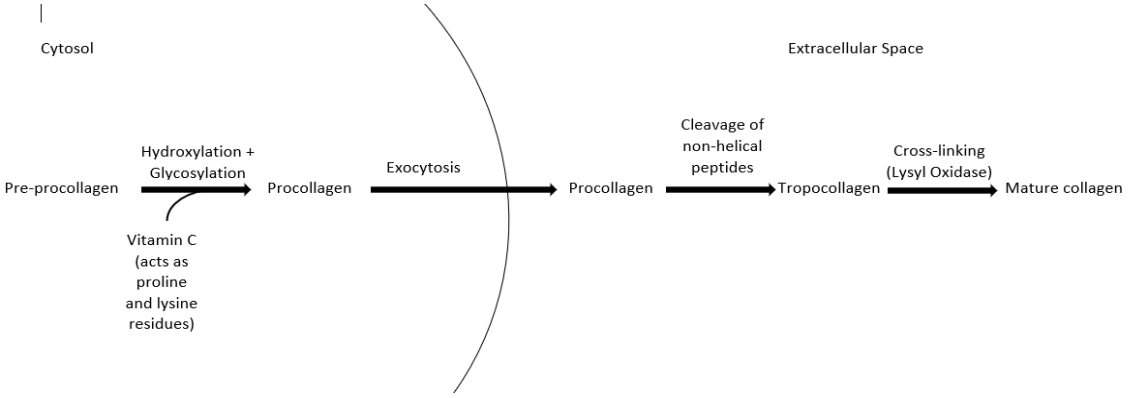
Models	Treatment doses	Mechanisms involved in the protective role of vitamin C	References
Mouse T-lymphocytes	250 µM for 14 days	-Development of mouse bone marrow-derived progenitor cells to T-lymphocytes *in vitro* and *in vivo*. -Enhancement of T-cell maturation -Enhances the selection of functional TCRαβ -Increases genes encoding the co-receptor CD8 as well as the kinase ZAP70	[51]
Bone marrow Stromal cells	250 µM for 24 h	-Regulate autophagy by reducing oxidative stress -Increases LC3B and decreases p62 protein.	[52]
Human astrocytes	50 – 200 µM for up to 30h	-Lowers and stabilizes the intralysosomal pH following the utmost lysosomal hydrolases/autophagy activation	[53]

EFFECTS OF VITAMIN C ON PATHOPHYSIOLOGIES ON ANIMAL AND HUMAN MODELS

Pharmacological effects of Vitamin C on various pathophysiological conditions evaluated using animal and human models

Models	Treatment doses	Mechanisms involved in the protective role of vitamin C	Reference
Guinea pigs	0.5 mg for 24h	-Phagocytosis/ROS generation, proper leukocyte chemotaxis	[54]
Sepsis patients	400 mg/day	-Improved neutrophil chemotaxis, and reduced caspase 3 expression	[55]
Gulo knockout mice infected with influenza virus	3.3 g/L Sodium L-ascorbate for 3 weeks	-Decreases synthesis of pro-inflammatory cytokines, TNF-α and IL-α/β in the lung and increases number of NK cells -Increases the level of IFN-α/β	[56, 57]
Polymicrobial peritonitis in Gulo knockout mice	200 mg/kg	-Decreases synthesis of TNF-α and IL-1β by isolated neutrophils	[58]
Prospective, controlled study of students	1,000 mg doses 3 times daily	-Relieves cold and flu symptoms -Prevents the symptoms or reduce viral infection risk	[59, 60]
Hypercholesterolemia patients	500 mg/d (for minimum 4 weeks)	-Significant decrease in serum LDL cholesterol and triglyceride concentrations	[61]
Patients with COVID-19	10 – 20 g/day (given over a period of 8 – 10 h)	-Improves oxygenation index in real-time	[62]

Steps of collagen synthesis displaying the importance of vitamin C early in the synthetic pathway, where it is used by proline and lysine hydroxylases to create procollagen



Vitamin C trials in patients with pneumonia, sepsis and severe COVID-19.

Patients	Intervention Dose (Duration)	Patient Outcomes	Refs.
Pneumonia			
Pneumonia/bronchitis (*n* = 57):	Oral vitamin C (28 day):	↓ respiratory symptom score in most severely ill	[63]
• **Placebo (*n* = 29)**	0 g/day	17% mortality in placebo group	
• **Treatment (*n* = 28)**	0.2 g/day	4% mortality in treatment group	
Pneumonia (*n* = 140):	Oral vitamin C (10 day):	↓ hospital length of stay:	[64]
• **Control (*n* = 70)**	0 g/day	24 days in control group	
• **Low dose (*n* = 39)**	0.25–0.8 g/day	19 days in low dose group	
• **High dose (*n* = 31)**	0.5–1.6 g/day	15 days in high dose group	
Sepsis			
Sepsis and ARDS (*n* = 167):	IV vitamin C (4 day):	X systemic organ failure score	[65]

• **Placebo (*n* = 83)**	0 mg/kg bw/day	X C-reactive protein, thrombomodulin X ventilator-free days ↓ 28 day mortality ↑ ICU-free days ↑ hospital-free days	
• **Treatment (*n* = 84)**	200 mg/kg/day		
Septic shock (*n* = 100):	IV vitamin C (until ICU discharge)	↓ vasopressor duration ↓ ICU length of stay X length of mechanical ventilation X renal replacement therapy X ICU mortality	[66]
• **Placebo (*n* = 50)**	0 g/day		
• **Treatment (*n* = 50)**	6 g/day		
Septic shock (*n* = 28):	IV vitamin C (3 day):	↓ norepinephrine dose and duration ↓ 28 day mortality X ICU length of stay	[67]
• **Placebo (*n* = 14)**	0 mg/kg bw/day		
• **Treatment (*n* = 14)**	100 mg/kg bw/day		
Severe sepsis (*n* = 24)	IV vitamin C (4 day):	↓ systemic organ failure score ↓ C-reactive protein, procalcitonin, thrombomodulin	[68]
• **Placebo (*n* = 8)**	0 mg/kg bw/day		
• **Low dose (*n* = 8)**	50 mg/kg bw/day		
• **High dose (*n* = 8)**	200 mg/kg bw/day		
Severe COVID-19			
Critical COVID-19 (*n* = 54)	IV vitamin C (7 day):	X ventilation-free days ↑ PaO_2/FiO_2 ↓ Interleukin-6 ↓ 28 day mortality in patients with SOFA scores ≥ 3	[69]
• **Placebo (*n* = 28)**	0 g/day		
• **Treatment (*n* = 26)**	24 g/day		

ARDS—acute respiratory distress syndrome; COVID—coronavirus disease; FiO_2—fraction of inspired oxygen; IV—intravenous; PaO_2—partial pressure of oxygen; SOFA—sequential organ failure assessment; ↓—decrease; X—no change. A part of this table has been reproduced from.[72]

ROLE OF VITAMIN C IN DIABETES MELLITUS

Stress generation linked to the increase of both types of diabetic hyperglycemia produced ROS in the cell, and triggered OS.[73] Studies showed that vitamin C may reduce the risk of developing diabetes mellitus (DM). There is a negative correlation between the vitamin C levels in plasma and the risk of type 2 DM.[75-79]

ROLE OF VITAMIN C IN CARDIOPROTECTION

The risk of coronary heart disease (CHD) can be significantly decreased by consuming a lot of vitamin C.[79] Vitamin C reduces the release of microparticles produced from endothelial cells in the therapy of congestive heart failure patients. Vitamin C therapy reduced apoptosis in cultured endothelial cells by obstructing oxidised low-density lipoprotein (LDL) and inflammatory cytokines.[79-85]

ROLE OF VITAMIN C IN KIDNEY PROTECTION

SARS-CoV-2 can infect non-respiratory organs; hence the kidney is regarded as a high-risk organ in COVID-19.[86] In the treatment of anaemia in chronic renal disease, vitamin C may be helpful.[86-89]

ROLE OF VITAMIN C IN CANCER

Recent research has shown that millimolar doses of vitamin C may be able to kill cancer cells.[90] Vitamin C may kill cancer cells because of its pro-oxidant properties.[91]

VIRAL, BACTERIAL, PROTOZOAL AND FUNGAL INFECTIONS

Viruses, bacteria, protozoa, and fungus are just a few of the pathogens that vitamin C is known to defend against.[92] The importance of this nutrient with an abundance of health advantages was highlighted by the absence of a specific vitamin, such as vitamin C, which can result in scurvy linked to pneumonia.[94] Undefined are the theorised ways through which a virus can cause a subsequent bacterial infection. However, given on its anti-microbial capabilities as they have been described thus far, vitamin C may be a potential supportive treatment option to tackle this catastrophic tragedy. Vitamin C, for instance, has been shown to be effective in preventing the growth of microorganisms such Candida albicans, Entamoeba histolytica, -hemolytic streptococci, Mycobacterium TB, and Fusobacterium necrophorum.[94] Vitamin C has antimicrobial and anti-biofilm properties. When given vitamin C (10 mg/ml), Escherichia coli and Klebsiella pneumoniae that had been isolated from infected patients grew much less.[95] In contrast, vitamin C had direct antibacterial activity against Enterococcus faecalis and Staphylococcus aureus at lower doses (0.15 mg/mL).[94] Additionally, vitamin C (8 to 16 g/mL) substantially prevented the growth of methicillin-resistant S. aureus (MRSA) biofilm.[97] Vitamin C slightly slowed the development of the E. coli ATTC 11775 strain.[98] Lactic acid and vitamin C administration stopped the growth of the E. coli O157:H7 strain.[99] Thus, the antibacterial effectiveness of vitamin C may differ depending on the type of bacteria and the different concentrations. Furthermore, vitamin C co-administered with other substances, such epigallocatechin gallate, which increased antibacterial activity, effectively suppressed multidrug-resistant bacterial species.[100]

Several different types of viruses commonly cause upper respiratory infections and common colds.[100] Following vitamin C therapy, a reduction in the frequency of common colds has been noted in British men; however, the processes by which this occurs are unclear.[101] A

prospective, controlled trial of students who received vitamin C revealed similar outcomes.[102] The favourable impact of vitamin C against the parainfluenza infection was suggested by a study in which vitamin C-treated marmosets were less likely to contract the parainfluenza virus than the control animals.[103] The administration of oral ascorbic acid in conjunction with prophylactic anti-viral agent treatment may reduce the likelihood of recurrence, according to a retrospective investigation on the impact of ascorbic treatment on patients with herpes simplex virus-induced keratitis.[104] Patients who were clinically infected with the Herpes Zoster virus responded well to intravenous vitamin C therapy.[105-106] Following intravenous vitamin C therapy, patients with ARDS who tested positive for enterovirus and rhinovirus recovered well.[107] The chicken's respiratory system is impacted by avian coronaviruses including the infectious bronchitis virus (IBV), a gammacoronavirus.[108] Following ascorbic acid therapy, the pathological lesions in chicks with IBV can be diminished.[109] Pre-exposed chick-embryo ciliated tracheal organ (CETO) cultures showed greater resistance to IBV infection, according to research by Atherton et al.[110]

CONCLUSIONS

Vitamin C contains strong anti-oxidant and anti-inflammatory properties that lower the risk of tissue damage caused by oxidative stress and diminish the cytokine storm, an overactive inflammatory response. It's interesting to note that treating COVID-19 patients in China and the US with a high dose of IV vitamin C has had positive outcomes. Additionally, there were no side effects associated with using large doses of vitamin C for a brief period of time. Therefore, given the pharmacological properties of vitamin C and its safety profile at large dosages, we recommend including vitamin C in the COVID-19 therapy protocol—especially if current RCTs that are listed on clinicaltrials.gov yield promising results soon. By boosting interferon synthesis and promoting lymphocyte proliferation, vitamin C enhances the host's defence against viral infection. It has been demonstrated that vitamin C can help prevent other respiratory infections and treat some severe COVID-19 problems, but further research is needed to demonstrate its effectiveness as a treatment. To guarantee the immune system is working at its best in case of exposure or infection with the coronavirus, it is currently advised to maintain a sufficient daily intake of vitamin C through sources like citrus, vegetables, and potatoes or through vitamin C supplements. High-dose therapy for moderate-to-severe infections should only be used in conjunction with therapies that have been more successful in the past, like corticosteroid, antibody, and antiviral therapy.

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