

The Review Of The Effects Of Vitamin C On The Management Of COVID-19

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Abstract

Background: Over the past 1.5 years significant advances in the treatment of Covid-19 have emerged. Please reword to reflect this change. Among the variety of suggested materials to aid patients regarding COVID-19, we chose Vitamin C, as it offers antioxidant functions and beneficial effects on the immune system. In this study, we aim to review the function and application of Vitamin C in body health during COVID-19 infection and elucidate the controversies around its efficacy against coronavirus infection.

Methods: We meticulously searched the relevant articles (n = 153) from PubMed, Scopus, Embase, databases according to the aimed keywords (COVID-19, Vitamin C, Treatment, Management).

Results: Supportive supplements are reasonable methods in countering the pandemic along with clinical therapy. Furthermore, Vitamin C helps prevent septic shock and further organ failure.

Discussion: We believe that our review demonstrates the highlights of one of the most important supplements in the disease relief.

Keywords: Vitamin C; Supplement; Alternative Medicine; Management; COVID-19

Introduction

In December 2019, the novel agent that caused severe acute respiratory syndrome (SARS), with a steep prevalence rate was reported in Wuhan, Hubei, China. After molecular evaluation, scientists found the novel coronavirus, which was then named and reported to the World Health Organization (WHO) as SARS-CoV-2 or 2019-nCoV. Immediately after, the WHO officially declared COVID-19 as an epidemic [1]. The main clinical characteristic of severe COVID-19 is SARS accompanied by dyspnea, dry cold, fever, and bilateral lung ground-glass opacity on CT imaging [2]. The entrance of COVID-19 initiates damage via its receptor, angiotensin-converting enzyme 2 (ACE2), to alveolar epithelial cells, which leads to the release of inflammatory cytokines (cytokine storm) that affect immune cells and pulmonary vascular endothelial cells [3, 4]. Also, lower respiratory tract cells, including alveolar macrophage and alveolar epithelial cells, are extremely susceptible to infection.

During the acute viral invasion, diffuse alveolar damage is initiated with prominent hyperplasia of pulmonary epithelial cells besides the appearance of activated alveolar and interstitial macrophages. Such manifestations indicate increased host immune response leading to alveolar damage [5]. Murine studies have shown over-activated residue immune cells due to the release of immune mediators, especially interferon type 1, which leads to extensive lung inflammation, summons more pathogenic sp inflammatory macrophages, and increases the

severity of SARS [6, 7]. Surprisingly, even faster than immune cells, the rapid kinetics of COVID-19 replication in the lower respiratory system trigger septic shock and further organ failure. Activation of effector immune cells, amongst which macrophage is a primary cell, may cause the release of chemicals such as lactic acid. This event could attenuate the immune response through decreasing interferon type 1, which is essential for viral clearance [8]. Therefore, a mediated element must exist in cooperation with immune cells to achieve adequate protection against viral infection.

Several studies have surveyed the effect of supplements as potential alternative therapeutic agents for COVID-19. Among them, Vitamin C, also known as ascorbic acid and ascorbate, is a water-soluble vitamin found in many foods. It carries out a distinct antioxidant function because of its unique redox potential. Vitamin C is stated that contributes to disease prevention and health promotion because of its significant role in the function of different body organs, including the cardiovascular system, central nervous system, digestive system, liver, skin, and eyes, etc. [9, 10].

Why vitamin C?

Vitamin C was discovered in the early 1900s, due to Scurvy, a disease caused by vitamin C deficiency, which took the lives of many sailors in the early 1900s, is linked to pneumonia. Subsequent studies showed that predisposition to infection, especially in the respiratory system, leads to relatively higher mortality in various age groups with Vitamin C deficiency. This association could be explained by the relationship between infection and dose-concentration of Vitamin C [11]. Furthermore, Vitamin C reduces oxidative stress caused by infections as well as effects on the immune system (e.g., phagocytes, maturation of T-cells, phagocytes, etc.) [11]. In the molecular study about the role of Vitamin C in the activation of effector cells, it has been revealed that Vitamin C can inhibit the inflammatory hyperactivation of myeloid and lymphoid cells that lead to severe sepsis and organ failure [12].

The anti-viral role of Vitamin C in the respiratory system

Pneumonia is the most common infection of the respiratory system in which lung cells are damaged because of inflammation. Typical symptoms include chest pain, fever, dry cough, and breathing difficulties. Viral infection by various viruses such as influenza, parainfluenza, rhinovirus, respiratory syncytial virus, adenovirus, and coronaviruses cause pneumonia [2, 13]. The infection starts from the upper respiratory tract, then moves into the lower sections, in which immunoglobulins and complement proteins are responsible for lower airway protection [14]. However, virus invasion may cause lung damage. In this stage, both innate and adaptive immune cells cause inflammation, which leads to lung damage and damage to other organs, including the kidneys [15], heart [16, 17], brain [18], bones [19], and the liver [20].

In different parts of the body, including the respiratory system, foreign microorganisms (e.g., virus and bacteria), can induce illness that leads to unfavorable health conditions [9]. Studies have shown consumption of high dose Vitamin C can prevent the proliferation of viruses in the respiratory system [21]. In vivo mouse studies on the role of Vitamin C in respiratory viral infections have demonstrated that mortality rates in the mouse group that could not produce Vitamin C are higher than the group that produced Vitamin C normally [22-24]. Another study mentioned that even though few members of the normal mouse group died due to viral pneumonia, the viral load in the lung was significantly lower than the group that was unable to produce Vitamin C. The probable cause of the effect of Vitamin C may be due to its inhibitory effect on the spread of the virus from the upper respiratory tract to the lower respiratory tract. Also, Vitamin C helps the airway epithelium maintain fluidity on their surface, as dryness of the epithelium aids the proliferation of viruses, which cause the high possibility of viral invasion. Another interesting finding of the study is that the level of interferons (INFs) in the bronchoalveolar lavage fluid was considerably lower in the Vitamin C insufficiency group, despite high levels of proinflammatory cytokines, such as IL-1(α and β) and TNF- α , as well as inflammatory cells. As we know, INFs are critically important in the defense against viral infection [25].

The findings have found a noticeable lower incidence of pneumonia in people receiving routine Vitamin C supplements. Despite the different doses of Vitamin C consumption, nearly all of the studies agree that use of

Vitamin C is beneficial for enhanced immune system function [26]. Furthermore, many studies have revealed the beneficial effect of Vitamin C consumption on treatment outcomes in cases with severe pneumonia. Vitamin C has proven effective in reducing respiratory symptoms, a shorter period of hospitalization, and normalization of imaging findings, biological, and blood characteristics [27].

Methods

The aim of this study was to review topic relevant studies on the role of Vitamin C in the relieving and reducing clinical symptoms of COVID-19. The history of searching and selecting databases has shown in figure1.

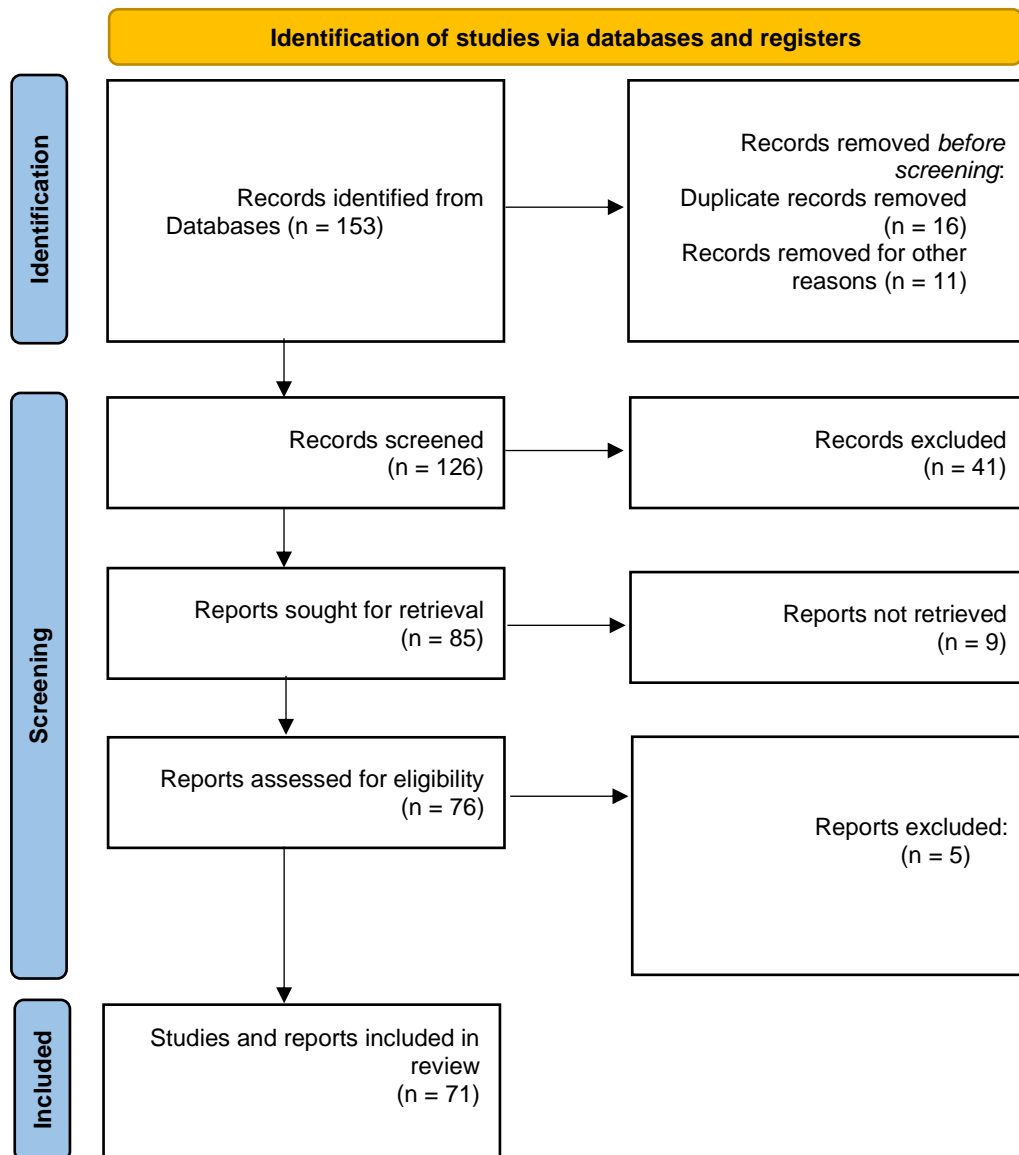


Figure 1: Summary of database evaluation and studying the relative studies

We searched various databases such as PubMed, Medline, Scopus, Embase, Web of Science, Scholar based of MESH and syntax, including Vitamin C, COVID-19, and SARS-CoV2 from beginning of COVID-19 infection up to May 2021. Inclusion criteria were to be fully detailed on the topic and have meticulous information from being infected to post infection clinical symptoms using Vitamin C in the treatment process. All the relevant articles were evaluated from their abstracts. We then go through the content and read one by one for getting the

demanding data. Exclusion criteria were irrelevant to the topic or not providing enough precise information. Some of the selected articles were excluded after reviewing the whole content. Details of study selection have been demonstrated in figure 1.

Results

Previous investigations about the role of Vitamin C in viral infections

In previous studies, the results of Vitamin C and its benefit in viral infections have been mixed. Carr investigated the role of Vitamin C in immune function and the promotion of health conditions [28]. Vitamin C possesses various antiviral properties and clinical benefits in patients with viral infections [29]. Vitamin C is said to reduce mortality in patients with sepsis [30]. Hemila and Chalker, in their meta-analysis, found that Vitamin C significantly reduced ICU length of stay and shortened the duration of mechanical ventilation, which is pivotal in the acute phase of viral disease [31].

In their retrospective analysis, Marik et al. emphasized the beneficial role of Vitamin C in the reduction of severe sepsis and septic shock [32]. However, a similar study by Litwak et al. dismissed the role of Vitamin C in decreasing ICU length of stay or hospital stay and mortality [33]. Patel et al., in their comprehensive molecular study, stated that oral consumption of antioxidants, such as Vitamin C, could attenuate hyperoxia-induced acute inflammatory lung injury. In other words, the use of antioxidants as a dietary supplement could decrease inflammation symptoms in patients receiving mechanical ventilation [34]. Cheng reviewed a series of literature and concluded that various antioxidants such as Vitamin C could improve the immune system, which, in turn, reduces predisposition to acute viral infections [35]. Law stated that restricting steroids and replacing antioxidants such as Vitamin E, Coenzyme Q-10, Vitamin C or Omega 3, 6, and 9 could be beneficial to promoting body cell regeneration in cases of organ damage such as acute lung inflammation [36]. Jahangir et al., in their meta-analysis noted that Vitamin C might act as an appropriate alternative supplement that boosts immunity [37]. Table 1 provides the summary of the main investigations on the role of Vitamin C in the treatment of viral infection.

Table 1. Summary of the primary studies on the role of Vitamin C in the treatment of viral infection

Authors	Study setting	Number of participants	Methodology	Results
Fowler AA 3 rd et al. [38]	Seven ICUs in the USA (September 2014 - November 2017); final follow-up: January 2018	167 patients with Sepsis and ARDS present hospitalized for less than 24 hours	IV Vitamin C (50 mg/kg in Dextrose 5% in water, n = 84) or placebo (Dextrose 5% in water only, n = 83) four times a day (QID), for 96 hours	No significantly improved organ dysfunction scores or alter markers of inflammation (CRP levels) and vascular injury (thrombomodulin levels) were observed
Won-Young Kim et al. [39]	Busan, Korea, June 2016 – January 2017 and June 2017 – January 2018	June 2017 – January 2018 (n = 53) and June 2016–January 2017 (n = 46)	PO administer 6g of Vitamin C per day (divided into four equivalent doses)	Use of Vitamin C was associated independently to decreased mortality The treatment group exhibited a significantly higher median improvement in the radiologic score on

				Day 7 compared to the baseline Administration of Vitamin C did not increase acute kidney injury or superinfection rates
Gonzalez MJ et al. [40]	Ponce, Puerto Rico 2018	A Case report study	IV Vitamin C (50 g sodium ascorbate in 1000 cc of lactated ringer's) for three days. Then, oral 2g CID	Vitamin C was effective against acute viral infection
Kim TK et al. [41]	The Republic of Korea, 2020	1,444 army recruits	695 participants (Vitamin C group) received Vitamin C (6000 mg/day), 749 participants (placebo group) received placebo (0 mg/day)	Vitamin C was shown to reduce common viral colds in Korean army soldiers
Anitra C. Carr et al. [42]	Christchurch Hospital, South Island, New Zealand (2020)	50 patients with COVID-19 (n = 50, 50% female, aged 57 ± 17 years)	Vitamin C levels were assessed in the plasma of samples using HPLC with electrochemical detection	Depleted Vitamin C status and increased oxidative stress was observed in patients with pneumonia
Hamidi Alamdari et al. [43]	Iran, 2020	25 ICU COVID-19 patients and 25 healthy individuals	methylene blue-vitamin C-N-acetyl Cysteine (MCN) were administered for 5 patients	Four patients out of 5 responded well to MCN treatment
Hernandez et al. [44]	Spain, 2020	Suggested the protocol of IV Vitamin C administration	Dose of Vitamin C: 0.2---0.5 g/kg/day (Single injection or divided into 2 or 4 administrations) Infusion rate: 0.25---0.5 g/min (between 1 and 4 h, depending upon the selected dose)	Because of antioxidant and antiviral properties of Vitamin C, IV infusion of up to 100g is safe
Khan et al. [45]	USA, 2020	Case report of critically ill COVID-19 patient	High dose IV Vitamin C injection 11g per 24h for 10 days	High dose administration of Vitamin C was associated to shorter ICU stay and rapid recovery

Zhang et al. [46]	China, 2020	Pilot trial of high dose intravenous Vitamin C in 56 critical ill patients	12 g/50 ml every 12h for 7 days at a rate of 12ml/h	However, it was FAILED to improve the endpoint of improved mechanical ventilation – but did improve oxygenation as measured by PaO ₂ /FiO ₂
Hiedra et al. [47]	USA, 2020	A case series of 17 who received IV Vitamin C for COVID-19 disease	Mean time of IV Vitamin C injection was 3 day (0-11 days)	Demand for fraction of inspired oxygen (FIO ₂) and inflammatory markers (D-dimer and Ferritin) were decreased

Discussion

COVID-19 and Vitamin C

Various opinions exist regarding the role of Vitamin C in reducing the signs and symptoms of viral infection. Vitamin C possesses a variety of beneficial biological properties, many of which are related to promoting the immune system functions. In cases of severe viral infection, it has been suggested that intravenous administration of Vitamin C could be beneficial to enhancing vitamin level which helps to defend body against infections.

Experimental investigations have shown the beneficial effects of Vitamin C on patients with COVID-19. Arvinte et al. in clinical research reported that the serum level of Vitamin C in most of critically ill COVID-19 ICU patients was low, among which Vitamin C level was co-dependent risk factor for mortality [48]. Likewise, Chiscano-Camón et al. in their cohort study observed that the level of Vitamin C in patients with COVID-19 associated ARDS were extremely low [49].

There are controversies between clinician scientist for administration of Vitamin C in COVID-19. For example, Kretchy et al. in their pharmaceutical care practices of community pharmacists discussed medication management for COVID-19. They suggested that the consumption of popular remedies such as Vitamin C could patronize and promote body health conditions during the COVID-19 pandemic [50]. In addition, Ghosh and Giri in their review stated that COVID-19 is a double-edged sword and expressed pieces of advice for different communities, one of which was exercising a nutritious diet rich in Vitamin C to boost immunity [51]. On the other hand, Qian et al. in the cross sectional population-based telephone survey established that taking Vitamin C was considered as misinformation by medical experts. They believe that taking Vitamin C has neither rational reasoning nor confirmed study verifies relative topic and it is only proved wrong rumor [52]. Likewise, ESPEN experts have stated in their practical guideline for nutritional management that taking micronutrients such as Vitamin C should be assessed in and supplied for COVID-19 patients, but not directly recommended for treatment approaches [53]. Similarly, Mowbray in one letter has dismissed its useful role for relief of COVID-19 symptoms [54].

Other examples of controversies in COVID-19 studies are: Zhang and Liu listed Vitamin C as a potential intervention for COVID-19. They believe that nutritional supplements can act as potential alternative therapeutic elements to control the COVID-19 pandemic [55]. Interestingly, Mian and Khan highly recommend taking Vitamin C despite the lack of evidence [56]. However, EL Ghoch and Valerio revealed existing evidence claiming that Vitamin C can prevent, treat, or cure COVID-19 is limited and much debated [57]. Similarly, Conforti et al. stated that there exists no evidence of home remedies such as high doses of Vitamin C to protect or cure COVID-19 [58].

Feyaerts et al. answered the question that can we use Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19, and concluded that Vitamin C can reduce inflammatory mediators and oral low dose (1-2 g/d) maybe beneficial prophylactically, and in the sever COVID-19 conditions, a high-dose regimen can be used [59]. Hernández et al. discussed the usefulness of Vitamin C as an adjuvant therapy in critical COVID-19 patients. They expressed Vitamin C is a potent, simple, and low-cost antioxidant with no side effects, which would be a useful adjuvant to administer in severe cases [60].

Few reviews have tried to overview the various biological points of Vitamin C and its effects during COVID-19 viral infection. Erol et al. reviewed the benefits of Vitamin C for the treatment of COVID-19 patients. They stated that Vitamin C, on the one hand, can help the function of the immune system, while on the other hand, prevent sepsis and further complications. They also suggested high dose IV Vitamin C can reduce the symptom of systemic inflammation and maintain the innate immunity of alveolar epithelial cells. All in all, they summarized that Vitamin C acts as a prooxidant to attenuate pro-inflammatory mediator expression, that clears the fluid accumulated in the alveoli and improves the function of epithelial cells [12]. Similar review by Abobaker et al. overviewed the multiple pharmacological and biological characteristics of Vitamin C and discussed it is sensible to add it to COVID-19 management protocol [61]. Similarly, Hançer et al. reviewed possible beneficial effects of vitamin C on COVID-19 relief. They also concluded that high doses of Vitamin C reduce lung damage and therefore it can be used as a complementary supplement [62]. Another interesting review done by Colunga Biancatelli et al. consumption of Vitamin C with Quercetin has been reported to have a synergistic therapeutic effect for the prevention and treatment of COVID-19. They presented current evidence that both materials have synergic antiviral and immunomodulatory properties [63]. Carr and Rowe reviewed the most update registered intravenous Vitamin C monotherapy for COVID-19 disease. According to preliminary and observational and interventional studies on COVID-19 patients, they noted that Vitamin C administration likely improves disease outcomes. They also notified that because of safety profile, low cost, ease of mass production, consumption of this vitamin appears warranted [64]. Another review done by Holford et al. has focused on role of Vitamin C as an adjuvant therapy for COVID-19. In line with other mentioned reviews, they suggested that due to beneficial effects of Vitamin C, oral dose between 2-8g/day and IV injection for hospitalized and infected person could be worthwhile [65]. Furthermore, Farjana et al. reviewed the different roles of Vitamin C in alleviating the COVID-19 complications[66]. Despite positive reviews on beneficial effects of Vitamin C in COVID-19 symptoms relief, Abat et al. in their rapid review gived their opinions whether there are advantages of Vitamin C in controlling of disease exacerbation. They concluded that there is no direct available beneficial effect for IV administration of Vitamin C as an adjunctive treatment [67].

Regarding the management of COVID-19, Paudel et al. mentioned that, according to some evidence, high doses of intravenous Vitamin C could be beneficial for the treatment of sepsis [68]. In spite of above-mentioned beneficial effects of Vitamin C, it should be kept in mind that high doses of Vitamin C are associated with oxaluria and oxalate nephropathy in COVID-19 patients through exogenous conversion of ascorbic acid to oxalate and further kidney tubular injury [69]. Table 2 presents the summary of performed studies on the association between Vitamin C and COVID-19 disease.

Table 2: Summary of different study outcomes for the association between Vitamin C and COVID-19

Pros studies (Support)	
Arvinte et al. [48]	lower serum levels of Vitamin C were significantly low in most of critically ill COVID-19 patients
Chiscano-Camón et al. [49]	Extremely low level of Vitamin C in ICU COVID-19 patients
Kretchy et al. [50]	Administration of Vitamin C promotes body health during COVID-19 pandemic
Ghosh and Giri [51]	Give advice to community that use nutritious diet contains Vitamin C
Feyaerts et al. [59]	Vitamin C can reduce inflammatory mediators
Hernández et al. [44]	Vitamin C is useful antioxidant with no side effects which can be used as an adjuvant therapy

Erol et al. [12]	Vitamin C acts as a prooxidant to attenuate pro-inflammatory mediator expression, that clears the fluid accumulated in the alveoli and improves the function of epithelial cells
Abobaker et al. [61]	Vitamin C is sensible to add for COVID-19 management protocol
Hançer et al. [62]	High doses of Vitamin C reduce lung damage
Colunga Biancatelli et al. [63]	Vitamin C and Quercetin have synergistic therapeutic effect on COVID-19
Carr and Rowe [64]	Vitamin C administration improved disease outcomes
Holford et al. [65]	Oral dose of Vitamin C between 2-8g/day and IV injection for hospitalized and infected person could be worthwhile
Farjana et al. [66]	By reviewing the different roles of vitamin C, they emphasized the usefulness of this substance in the COVID-19 disease
Zhang and Liu [70]	Listed Vitamin C as a potential substance for COVID-19 disease
Mian and Khan [56]	Despite lack of evidence, they suggested taking Vitamin C
Paudel et al. [68]	According to some evidence, high doses IV Vitamin C could be beneficial for treatment of sepsis
Cons (Lack of support)	
Qian et al. [52]	Taking Vitamin C is debated to have beneficial effect on COVID-19 relief
Barazzoni et al. [53]	ESPEN experts not directly recommended, but suggested to assessment in COVID-19 patients
Mowbray [54]	In the letter did not find the beneficial role of Vitamin C in COVID-19 symptoms
Abat et al. [67]	There is no direct confirmed beneficial effect of IV injection as an adjunctive treatment
EL Ghoch and Valerio [57]	Evidence for beneficial effect of Vitamin C is much limited
Fontana et al. [69]	Use of high doses Vitamin C were associated with oxaluria and oxalate nephropathy in COVID-19 patients

Conclusion

In this review, we considering writers' commentaries and viewpoints or scientific studies on the role of Vitamin C in relieving the symptoms of viral infections, especially COVID-19. Much of the literature has declared that the consumption of Vitamin C could aid the immune system against viral infections. Generally, it is believed that supplemental nutrition can promote health and strengthen the immune system to promote and help to expedite lung cell restoration. Although, due to the limited number of trials, expanded treatment strategies based on Vitamin C could be performed to establish a promising treatment approach.

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Conflict of interest

The authors declare no potential conflict of interest

Ethical approval

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Author contribution

V.S contributed to the conception and design of the research; Sh.Sh contributed to the design of the research; A.A contributed to the acquisition and analysis of the data; A.A and Gh.G contributed to the interpretation of the data; and V.S and Sh.Sh drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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