PharmaNutrition 12 (2020) 100190

Contents lists available at ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu

Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome

Alberto Boretti*, Bimal Krishna Banik

Prince Mohammad Bin Fahd University, P.O. Box 1664, Al Khobar, 31952, Saudi Arabia

ARTICLE INFO

Keywords:
Vitamin C
Severe acute respiratory syndrome coronavirus
Antiviral agents
Covid19
Cytokines

ABSTRACT

The recent outbreak of Covid19 has required urgent treatments for numerous patients. No suitable vaccines or antivirals are available for Covid19. The efficiency against Covid19 of WHO therapies of choice, that are two antivirals developed for other pathologies, is controversial. Therefore, alternative approaches are required. Intravenous (IV) Vitamin C (Vit-C) has emerged as one of the other alternatives for this purpose. Here we review the effects of IV Vit-C on the immune system response, the antiviral properties of IV Vit-C, and finally the antioxidant properties of IV Vit-C to specifically address the cytokines' storm characteristic of the Acute Respiratory Distress Syndrome (ARDS) that occur in the later cycle of the Covid19 infectious disease.

1. Introduction

The recent outbreak of Covid19 has required urgent treatments for numerous patients. The Covid19 originated in Wuhan, China has spread to other continents and has caused significant harm to the public. Fig. 1 represents a transmission electron microscope image of Covid19 along with a 3D structure of coronavirus. No suitable vaccines or antiviral drugs exist against Covid19. At the time of writing (15 March 2020), Coronavirus cases were already 173,085 (+19 % over the last 24 h, +5% the day before), with 6664 deaths (+23 % over the last 24 h, +6% the day before) vs. 77,784 recovered (+6% over the last 24 h), with some improvements in China. However, the condition is deteriorating in Western Europe, especially Italy. No cure for Covid19 is known at this time. In addition to administering oxygen, current treatments recommended by the World Health Organization (WHO) for the serious, critical cases of Covid19 include Remdesivir, Kaletra, and Kaletra plus Interferon (France24, "*Conquering the coronavirus: the most pressing goal for these researchers in Paris*", youtu.be/L0wRSKnIErk). Remdesivir is an antiviral nucleotide developed as a treatment for the Ebola virus and Marburg virus infections. Kaletra is a combination of Lopinavir and Ritonavir (LPV/r). This is also used as antiviral nucleotide analogs developed for the treatment of HIV/AIDS. The third option is a combination of Kaletra with Interferon. Interferons are signaling proteins (cytokines) that infected cells produce and release in response to viruses. Interferons activate other cells of the immune system so that a stronger immune system response can be achieved. Interferon alphas are specifically recommended for viral infections and some cancers. The efficacy of these processes for Covid19 is controversial. Therefore, alternative approaches are urgently needed.

In China, the death rate was peaked at 3% a few weeks ago but is now declined to 0.7 %. Good results are obtained using Interferon Alpha 2B (IFNrec) without any combination with Kaletra. The use of Intravenous (IV) Vitamin C (Vit-C) has shown promise in this area in China. The IV Vit-C (or Ascorbic acid) protocols are mentioned in clinicaltrials.gov, for Covid19 and other pathologies. Shanghai now utilizes IV Vit-C in the treatment for Covid-19. Many physicians in China have identified promising results using IV Vit-C against Covid19. Thus, there is a need to urgently review the uses of IV Vit-C, pre- and post-infection, and during different stages of the infection. IV Vit-C is helping to develop a stronger immune system response, reducing the cytokines storm, or increasing antiviral activities through other unknown mechanisms.

Perhaps, the reduction of the cytokines storm in the late stages of the Covid19 infection is the most significant application of IV Vit-C. Covid19 pneumonia is a complex medical disorder with high morbidity and mortality rate. This causes severe lung injury that results in Acute Respiratory Distress Syndrome (ARDS), a life-threatening lung disorder. This process prevents the necessary oxygen to enter into the lungs and ultimately causes death. Coronaviruses increase oxidative stress that promotes cellular malfunction and ultimately results in organ failure. It is believed that pulmonary failure (ARDS) is the principal cause of Covid19's action on humans. This helps to increase oxidative stress considerably because of the generation of free radicals and cytokines. This process finally leads to serious cellular injury, organ failure and

* Corresponding author.
E-mail address: a.a.boretti@gmail.com (A. Boretti).

https://doi.org/10.1016/j.phanu.2020.100190
Received 31 March 2020; Received in revised form 5 April 2020; Accepted 6 April 2020
Available online 21 April 2020

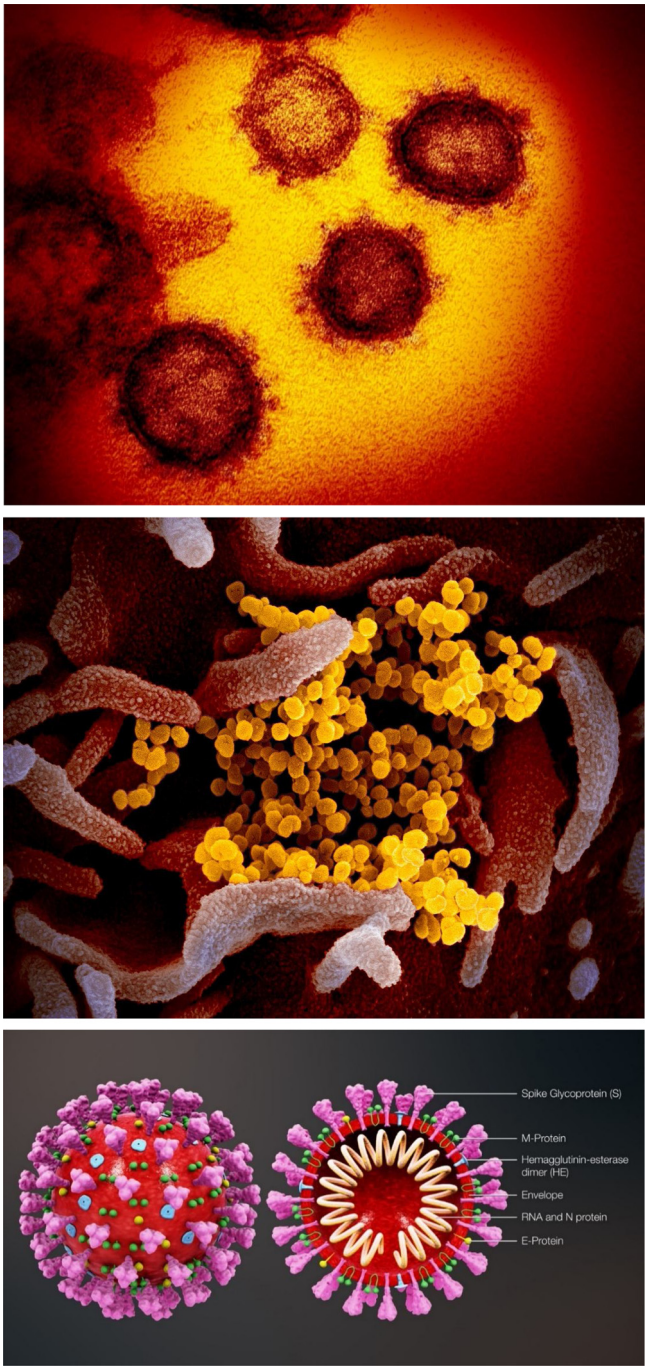

Fig. 1. Top, novel Coronavirus SARS-CoV-2. This transmission electron microscope image shows SARS-CoV-2—also known as 2019-nCoV, the virus that causes COVID-19. isolated from a patient in the U.S., emerging from the surface of cells cultured in the lab. Credit: NIAID-RML.CC BY 2.0. sv.wikipedia.org/wiki/Severe_acute_respiratory_syndrome_coronavirus_2#/media/Fil:SARS-CoV_with_corona.jpg.
Middle, Novel Coronavirus SARS-CoV-2 This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the U.S., emerging from the surface of cells (pink) cultured in the lab. Credit: NIAID-RML. CC BY 2.0.
sv.wikipedia.org/wiki/Severe_acute_respiratory_syndrome_coronavirus_2#/media/Fil:SARS-CoV-2.jpg Bottom, 3D medical animation still shot showing the structure of a coronavirus. CC BY-SA 4.0.
sv.wikipedia.org/wiki/Severe_acute_respiratory_syndrome_coronavirus_2#/media/Fil:3D_medical_animation_coronavirus_structure.jpg.

death. The administration of anti-oxidizing agents along with proven conventional supportive therapies is believed to have an important role in controlling these medical situations. Appropriate vaccines and antiviral drugs for the Covid19 epidemic are not available. IV Vitamin C and other antioxidants are extremely good agents for ARDS. These can be applied clinically. Importantly, high dose IV Vit-C is safe and effective. In this paper, we review the use of high-dose Vit-C as an efficient method of treatment for patients with cancers and infections.

The antiviral properties of Vit-C help to reduce symptoms and mortality in children and adults [1–4]. The antiviral activities of ascorbic acid was known and it was published almost 80 years ago [5–9] when scientists were involved in work on poliomyelitis. Moreover, the use of ascorbic acid as a medicinally crucial agent against various diseases was also well established [10–21]. Applications of Vit-C are found in poliomyelitis [22–26]. Many other uses of Vit-C include hepatitis, herpes, chickenpox and measles, infectious mononucleosis, trichinosis, urethritis, Antabuse, arthritis, and cancer. Vit-C is also helpful for the treatment of elevated cholesterol and arteriosclerosis, [27–32], corneal ulcers, glaucoma, burns, heatstroke, sunburn, slipped disc, toxins, and heavy metal poisonings [33–35]. The appropriate clinically effective vaccines and specific antivirals may serve effectively if they are available. Considering the current situation, the use of Vit-C as an antiviral agent should also be considered. Notably, Vit-C can be used alone or in combination with other available medicines to exert positive synergistic effects. Here we review the principal mechanism of actions of IV Vit-C that helps to make the immune system stronger, reduces the cytokines storm and inhibits oxidative processes. Under the first criteria, literature knowledge on cancer treatment will be reviewed first. Then, the antiviral properties will be reviewed, with focusing on the reduction of the oxidative pathways typical of the Covid19 ARDS.

2. Cancer treatment

A review of laboratory, animal and human studies and current clinical trials is provided regarding cancer treatments [36]. Vit-C is a crucial nutrient with redox properties, a cofactor of numerous enzymes, and it plays an important role in the synthesis of collagen [37]. A deficiency of Vit-C may result in scurvy [38]. Scurvy can cause collagen structure narrow and thin. It has been found that normal healthy situation can be maintained with the administration of Vit-C. In the mid-20th century, a study hypothesized that cancer can originate due to the alterations of the structures in connective tissues caused by Vit-C deficiency [39]. A review suggested that a high-dose of ascorbic acid can enhance host resistance. This study also identified the use of ascorbic acid in cancer therapy [40]. In general, Vit-C is synthesized from isomeric sugars D-glucose or D-galactose by numerous plants and animals. Interestingly, humans lack the enzyme L-gulonolactone oxidase which is required for ascorbic acid synthesis. On this basis, humans need Vit-C through food or other supplements [37].

Vit-C is an essential nutrient with redox properties in normal physiological situations [36]. Some cancer patients were treated successfully with high-dose of oral and/or IV Vit-C. However, two early randomized placebo-controlled studies of high-dose oral Vit-C (10 g/d) indicated no significant effects against cancers. These studies indicated marginal medical benefits between ascorbate- and placebo-treated groups. Laboratory experiments reported that high-dose of Vit-C can decrease cell proliferation in prostate, pancreatic, colon, mesothelioma, and neuroblastoma cancer cell lines. Studies of Vit-C combined with other medicines in animal models demonstrated inconclusive results. Importantly, IV Vit-C was well-tolerated in clinical trials. An IV administration of Vit-C (500 mg) was found to be more effective than oral administration since a higher blood concentration of ascorbate was found through the IV route. A study with Vit-C as ascorbate versus ascorbate formulations along with standard cancer therapies was performed in clinical trials. Two studies of high-dose Vit-C confirmed a better quality of life and fewer cancer-related toxicities. These results

from preclinical and clinical trials of high-dose Vit-C with and without standard cancer therapies are note-worthy. However, it may be challenged that these investigations have a few shortcomings.

The use of high-dose Vit-C (IV and oral) for the management of cancer was started five decades ago [41]. The application of Vit-C therapy in the treatment of various cancers was promoted [42,43]. For example, two clinical trials of Vit-C were conducted many years ago [44,45]. Pharmacokinetic experiments identified considerable differences in the maximum achieved blood concentrations of Vit-C. It was found that the nature of the route of delivery was relevant. For example, if Vit-C was taken orally, plasma concentrations are controlled with a peak achievable concentration of less than 300 μM. However, this control was bypassed with IV administration of the vitamin, resulting in a very high level of Vit-C plasma concentration (up to 20 mM) [46,47]. Additional research suggested that pharmacological concentrations of ascorbate as achieved with IV administration may result in cell death in numerous cancer cell lines [48]. Health care practitioners who had participated in complementary and alternative medicine conferences in 2006 and 2008 were debated on the benefits/risks of high-dose IV Vit-C in patients. A total of 199 participants were chosen and out of which 172 were taken Vit-C. Specifically, IV Vit-C was recommended to fight against infection, cancer, and fatigue [49].

In the early 1970s, a case study was conducted with 50 cancer patients who were taken a high dose of ascorbic acid [41]. Conventional therapies were applied to these patients, but these were not successful. On this basis, these patients were recommended to take ascorbic acid. Different doses and schedules were used. For example, some patients were given IV ascorbic acid (10 g/day for 10 successive days), a few were given higher dose amounts, and some were chosen to give oral ascorbic acid (10 g/day) or a combination of both. A wide variety of responses were found. Dome of them had no or minimal response and some of them had tumor regression and tumor hemorrhage. Despite this important observation, a lack of control study prevented making any conclusion on the health benefits of ascorbic acid treatment. From a limited study published in 1975, it is apparent that one of the patients experienced tumor regression [60]. The patient who had reticulum cell sarcoma exhibited improvement due to the treatment with ascorbic acid. A reduction of the daily dose of ascorbic acid was not helpful since symptoms of the disease appeared. Notably, remission was successfully achieved again after the same patient was given a higher initial dose of ascorbic acid.

A larger study of terminal cancer patients treated with ascorbate was conducted in 1976. In this investigation, 100 terminal cancer patients [41] were given ascorbate through an acceptable and scientific way (10 g/day for 10 days IV, then repeated orally). The health conditions of these patients were evaluated concerning 1000 matched control patients from the same clinic. Interestingly, the average survival time for ascorbate-treated patients was considerably much higher (300 days) than that of the matched control group [42,43].

Two randomized investigations using placebo-controlled trials were performed. In these studies, cancer patients were taken either 10 g of oral Vit-C or placebo daily until signs of cancer go away. At the end of these investigations, no significant differences in clinical results were found between the two ascorbate- and placebo-treated groups [44,45].

A study disclosed three case reports on cancer patients who received IV Vit-C as their main medicines. During Vit-C uptake, the patients were also given other materials including vitamins, minerals, and botanicals. It was claimed that the cases are analyzed following the National Cancer Institute (NCI) Best Case Series procedures. Histopathologic tests found weak prognoses for these patients. But the survival period of these patients went up after being treated with IV Vit-C [61]. Vit-C was given from 15 g to 65 g, once or twice a week, for several months to these patients. Two studies demonstrated that IV Vit-C treatment helps to improve the quality of life and decreases the side effects associated with cancer [62,63].

Systematic studies identified that the doses of Vit-C to volunteers or cancer patients can be up to 1.5 g/kg. No toxicity risks were seen (for example, glucose-6-phosphate dehydrogenase deficiency, renal diseases or urolithiasis). These studies identified that plasma concentrations of Vit-C can be much higher with IV administration than that of oral administration. The concentration was maintained for approximately 4 h [46,47].

A phase I study investigated the safety and efficiency of dual drug therapy by combining IV ascorbate with gemcitabine and erlotinib in stage IV pancreatic cancer patients. Fourteen subjects were evaluated in this study. The patients received IV gemcitabine (1000 mg for 30 min, once a week for 7 weeks), oral erlotinib (100 mg daily for 8 weeks), and IV ascorbate (50 g/infusion, 75 g/infusion, or 100 g/infusion 3 times per week for 8 weeks). No adverse effects were observed for ascorbic acid treatment. Five subjects received fewer than 18 of the proposed 24 ascorbate infusions. In three patients the disease was continued. Imaging tests were performed on nine patients to assess tumor size. This showed that the health situation was stable in each of them [64].

A 2013 phase I clinical investigation studied the effects of combining ascorbate with gemcitabine in the treatment of stage IV pancreatic cancer. During each 4-week cycle, patients were given gemcitabine weekly for 3 weeks and ascorbate for 4 weeks with a specific dose. This study found a progression-free and overall survival period. The combination of drug treatment was acceptable well [54].

In 2014, a phase I/IIA clinical trial measured the toxicities of two systems. The first one was combined IV ascorbate with carboplatin and the second one was ascorbate paclitaxel in stage III/IV ovarian cancer. More than 24 patients were chosen to receive either chemotherapy alone or chemotherapy and IV Vit-C. The chemotherapy was given for 6 months and IV Vit-C was continued for 12 months. Interestingly, IV Vit-C reduced chemotherapy-related toxicities [65].

A phase I/II clinical trial of high-dose IV Vit-C with numerous chemotherapeutic agents was conducted in 2015. This study was performed to evaluate multiple factors. Some important targets were to evaluate associated adverse effects, to determine the pharmacokinetic activities of Vit-C, to understand the clinical potential, to evaluate changes in mood and behavior and to assess the lifestyle [66].

A high-dose of IV Vit-C was analyzed in 14 patients. The procedures performed were tolerated well and were safe. A few temporary side effects were seen: increased urinary flow, thirst, nausea, vomiting, and chilling. It was important to note that an administration of chemotherapeutic agents did not alter the plasma concentration of Vit-C. A few patients were benefitted from this treatment because they experience temporary stable disease, demonstrate more activity with additional energy. However, since the group was small, no general conclusions from this study were drawn [66].

Recently, [67], a phase I study was evaluated to evaluate the safety, bioavailability, and efficiency of high-dose IV Vit-C in combination with chemotherapy regimens mFOLFOX6 or FOLFIRI. These were a combination of well-known agents: oxaliplatin, leucovorin, and 5-fluorouracil or leucovorin, 5-fluorouracil and irinotecan hydrochloride. This study was conducted on 36 patients with metastatic colorectal or gastric cancer. The principal aims were to evaluate the maximum-tolerated dose. Another goal was to determine the phase II dose of ascorbic acid with co-administration with mFOLFOX6 or FOLFIRI. Initially, all patients were given an identical chemotherapy treatment for 14 days with Vit-C infusions. Later, the concentration of ascorbic acid was altered for the dose-escalation investigation. This study demonstrated no dose-limiting toxicity. Therefore, a maximum-tolerated dose was not identified from this investigation. However, a dose of 1.5 g/kg for ascorbic acid was recommended for this phase II study. No adverse side effects were observed and the treatments were acceptable to the patients. Based on the success, a randomized phase III investigation is under progress. The goal of this study is to determine the clinical power of ascorbic acid against metastatic colorectal cancer in combination with mFOLFOX6 with or without bevacizumab [67].

Several studies were performed small doses of IV ascorbic acid

treatment (1000 mg) with arsenic trioxide regimens, and mixed results were obtained [68–70].

Clinical investigations of ascorbate in combination with arsenic trioxide were reported [36]. Patients with non-small cell lung carcinoma (NSCLC) and glioblastoma multiforme (GBM) were treated in two clinical trials [71,72]. The patients in both of these trials were undergone conventional therapy along with IV Vit-C. IV Vit-C was administered under radiation therapy and in the presence of temozolomide. The toxicity and overall survival rate of the patients were favorable. The NSCLC clinical trial was a phase II procedure that has 14 patients with advanced cancer. These patients were also given both chemotherapy and IV Vit-C. The results of this investigation were also favorable.

Many trials with IV Vit-C in a combination with other medicines are under active investigation. Accordingly, 5 trials are being conducted by scientists at Iowa University, 4 phase II studies and 1 phase IB/II trial. The 4 phase II clinical trials are focused to identify the efficiency of high-dose ascorbic acid combined with common anticancer molecules. These studies with ascorbate are also progressing with many cancer cell lines. These include studies on non-small cell lung cancer therapy under radiation therapy and in the presence of carboplatin and paclitaxel; metastatic pancreatic adenocarcinoma in the presence of gemcitabine and nab-paclitaxel; pancreatic adenocarcinoma in the presence of gemcitabine and radiation therapy, and glioblastoma in the presence of temozolomide and radiation therapy. Another phase IB/II trial is investigating the safety and clinical performance of high-dose ascorbate with radiation therapy against soft tissue sarcoma.

Numerous studies used IV ascorbic acid at a fixed dose of 1000 mg with various amounts of arsenic trioxide as anticancer therapy. It was expected that the pro-oxidant character of IV ascorbic acid can improve the effects of arsenic trioxide by a sensitization process of the malignant cells to arsenic's cytotoxic nature [72]. The combination therapies worked well. Some benefits against multiple myeloma were observed. However, the role of Vit-C in this was not determined [73–75]. In contrast, similar combination regimens were not effective and resulted in side effects, including the progression of the disease with particular cancer. Moreover, no anticancer effects against metastatic colorectal cancer [76] and metastatic melanoma were determined [77]. Since these trials were not placebo-controlled, the role of ascorbic acid to the results is unclear.

Intravenous (IV) high-dose ascorbic acid was well-tolerated in clinical trials [46], [78], [74], [71], [73], [64]. It was speculated that ascorbic acid may accelerate renal failure in patients with preexisting renal disorders [49]. Glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients were not good candidates to have high doses of Vit-C due to hemolysis [50–52]. Vit-C was able to improve the bioavailability of iron. A large dose of Vit-C was not recommended for patients with hemochromatosis [53].

Vit-C in high doses reacted with a few anticancer compounds. These interactions were detected in preclinical studies. A phase I clinical investigation examined the feasibility of using high-dose IV ascorbate and gemcitabine in stage IV pancreatic cancer patients. It was important to know that the combination formula was well tolerated by patients. No adverse effects were observed [54].

In vitro and in vivo animal studies indicated ascorbate can alter the mechanism of the drug. For example, ascorbate with bortezomib altered the action of the medicine as a proteasome inhibiting agent and blocked bortezomib-mediated cell death [55–57]. This interaction was observed with a low concentration of Vit-C (40 mg/kg/day) to animals. The cell culture study on blood plasma with Vit-C (1 g/day) also demonstrated a large decrease in bortezomib's growth inhibitory effect against multiple myeloma cells. The plasma of healthy volunteers was analyzed. Bortezomib growth inhibition on multiple myeloma cells was observed when a person takes 1 g of oral Vit-C per day. This amount had blocked the drug's inhibitory properties against the 20S proteasome [57]. On the other hand, a study that utilized mice harboring human prostate cancer cell xenografts did not find any good effect of oral Vit-C (40 mg/kg/day or 500 mg/kg/day) on the tumor growth inhibitory action of this medicine [58]. Studies showed that dehydroascorbic acid, an oxidized form of Vit-C alters the cytotoxic properties of some chemotherapy drugs [59]. But, the concentration of dehydroascorbic acid is found to be low in dietary supplements and foods.

Despite some controversial results over the years, Vit-C had proven to have anticancer effects when given intravenously at high concentrations [79]. Some reports on the anticancer activities of Vit-C were dependent on the use of immune-deficient mice. These studies were conducted to examine the direct effects of ascorbate on tumors. It was found that the effects of Vitamin C are much stronger in the presence of an intact immune system [79]. These observations suggested a combination treatment which requires evaluation in patients.

3. Treatment of viral infections

The antiviral properties of Vit-C were recently reviewed [80]. Vit-C was used for the treatment of hypovitaminosis C in malnourished patients. A combination of hydrocortisone, ascorbic acid, and thiamine (HAT therapy) worked well in the treatment of patients with sepsis and septic shock [81]. There were 29 ongoing or completed clinical trials with Vit-C administration in sepsis. The effectiveness of Vit-C in preventing common cold [82] and other health disorders was questioned [83,84]. The ascorbic acid therapy for acute inflammatory disorders was based upon numerous biological studies following many decades of research. The current interest in Vit-C focuses on bacterial sepsis and septic shock in patients. More than 300 scientific and clinical studies supported mechanistic data to use Vit-C against this disease [85,86]. Some other additional role of Vit-C in the treatment of viral diseases is also possible. The biological concepts and evidence for the use of Vit-C in viral infections are described here.

Numerous studies identified that Vit-C in high dosages is virucidal [83]. This conclusion was based on *in-vitro* experiments. In the presence of copper and/or iron, high doses of Vit-C showed virucidal activity. This was explained through the formation of hydrogen peroxide and other radical initiators [87,88]. Moreover, the low pH value of the system was responsible for the *in-vitro* antiviral effects of Vit-C. Despite these studies, the *in vivo* virucidal activity of Vit-C was not confirmed. It was well established that Vit-C is a powerful antioxidant and it can exert pro-oxidant effects at high concentrations. The generation of reactive oxygen species through the reduction of transition metal is possible [89]. It was found that a very high-dose of one sodium salt of ascorbic acid (90 mM) kills *Candida albicans in-vitro* through an iron-catalyzed Fenton reaction [90]. An iron chelator 2,2′-bipyridyl inhibited this effect. An experiment demonstrated that Vit-C can decrease the viral load of the Ebstein-Barr virus (EBV) [91]. This observation suggested multiple mechanisms are involved in Vit-C-controlled antivital therapy. The activity of antigens and load was reduced through pre-treatment of human foreskin fibroblast and endothelial cells with ascorbate before cytomegalovirus (CMV) infection [92]. This observation was failed to reproduce when ascorbate is added after the infection. The immunomodulatory activities of Vit-C were responsible for this effect. In general, Ascorbic acid is concentrated in leucocytes, lymphocytes, and macrophages [93,94]. Chemotaxis was improved by Vit-C [95–97]. The neutrophil phagocytic activity and oxidative death were also enhanced [95–97]. Lymphocyte proliferation was also accelerated [95–97].

The rate-determining last step of ascorbic acid biosynthesis in animals is L-Gulono-γ-lactone oxidase or the isomeric Gulo form. Mutations in the gene of this enzyme prevented anthropoid primates and guinea pigs to synthesize this molecule. The effects of Vit-C in viral infections were studied via a Gulo (-/-) knockout mice system. It was shown that nasal inoculation of the H3N2 influenza virus is fatal in Gulo (-/-) mice in comparison to wild type mice [97]. Anti-viral cytokine interferon (IFN)-α/β became lower. However, the viral titers in the lung of ascorbic acid-insufficient *Gulo (-/-)* mice became more abundant [97].

The pro-inflammatory cytokines, tumor necrosis factor (TNF), interleukin-1 (IL-1)-α/β, and infiltration of inflammatory cells was increased in the lung. These results were corrected in Gulo (-/-) mice repleted with ascorbic acid before viral exposure occurs. Most probably, an impaired phosphorylation process of signal transducers and activators of transcription (STATs) was responsible for the decreased generation of IFN in Gulo (-/-) mice [98]. It was found that Gulo (-/-) mice as compared to wild type mice have an impaired immune response with higher lung pathological dysfunction when exposed to influenza H1N1 virus [98]. It was shown that restraint-stressed mice with H1N1-induced pneumonia have a dose-dependent reduction of mortality in the presence of ascorbate. Histopathological lung sections also demonstrated reduced problems in the treated mice [99]. An administration of Vit-C was helpful to recover mitochondrial membrane potential and gene expression of pro-inflammatory cytokines. Ascorbic acid was reported to have clinical activity against numerous other viruses including poliovirus, Venezuelan equine encephalitis, human lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV) and rabies virus in addition to demonstrating activity against influenza and herpes virus [100–107].

It is known that most of the infections activate phagocytes with the generation of reactive oxygen species (ROS). The ROS has a key role in deactivating viruses. Some of the ROS harm the host cells that cause viral-induced host injury. Respiratory syncytial virus (RSV) infects the upper and lower respiratory tract in infants and children. RSV infection of airway epithelial cells accelerates ROS production and this inhibits the concentration of the lung antioxidant enzymes. The oxidant-antioxidant amount and proportion in cells are critical to RSV pulmonary toxicity [108]. Lung pulmonary inflammation and injury are considerably reduced by the administration of antioxidants [109]. Ascorbic acid is a powerful antioxidant and therefore, it scavenges oxygen free radicals and restores other cellular antioxidants. These include tetrahydrobiopterin and α-tocopherol [94]. The hypothesis that Vit-C may become beneficial in the treatment of viral infections is based on two concepts. Patients with infectious diseases do not have a sufficient level of Vit-C due to metabolic consumption [110]. Vit-C has immunomodulating properties in patients with viral infections. This is possible by increasing the production of α/β interferons and down-regulating the synthesis of pro-inflammatory cytokines. Despite that Vit-C have beneficial effects in viral infections no solid clinical data exists on this topic. Pauling suggested that Vit-C can be used for the treatment of the common cold. On this basis, most of the randomized controlled trials (RCTs') targeted the role of Vit-C in the prevention and treatment of the cold symptoms. In an analysis of 29 RCTs, Vit-C failed to reduce cold disease [82]. No consistent effects of Vit-C were observed also on the duration of colds in patients. Several studies, however, complicated the interpretation of these data.

Ascorbic acid may have clinical effects in patients with infections caused by herpes viruses. Herpes zoster (HZV) infection takes place due to the reactivation of the latent Varicella-Zoster virus (VZV). This is particularly predominant because of the loss of cell-induced immunity with age. The concentration of ascorbic acid in plasma is decreased in post-herpetic neuralgia patients compared to healthy persons [111]. An RCT study was conducted with 41 patients who were subjected to IV Vit-C (50 mg/kg on days 1, 3 and 5) or placebo [111]. It was found that those patients who were taken IV Vit-C have experienced less pain. In a non-blinded RCT, the role of ascorbic acid on acute herpetic pain and postherpetic neuralgia were evaluated [112]. Eighty-seven patients were given 5 g of IV ascorbic acid on the first, third and fifth days or placebo. Interestingly, a few differences between the groups were observed. The treated group with Vit-C demonstrated a lower incidence of postherpetic neuralgia and a lower pain score. Vit-C is mostly concentrated in the aqueous humor of the anterior chamber of the eye. A retrospective cohort investigation indicated that oral Vit-C reduced the risk of herpes simplex keratitis in combination with an oral antiviral drug [111].

It was concluded only a few months before the start of the CoV19 epidemic that there is an urgent need for novel research about the application of IV Vit-C, targeting the management of infectious diseases [80]. Influenza A virus causes epidemics and pandemics that kill thousands of people every year. Experimental studies demonstrate a beneficial effect of ascorbic acid against influenza. Patients with respiratory disorders due to infection by influenza were treated with histone acetyltransferase (HAT) without corticosteroids. Remarkably, these patients showed rapid improvement after the initiation of HAT. Corticosteroids, on the other hand, have a complex role in the treatment of infection. As a result, corticosteroids may not be a standard choice in patients with influenza A infection [113,114]. Effective clinical trials are necessary to investigate the use of Vit-C against infections due to influenza, RSV, herpes, and other viral illnesses.

A large dose of IV ascorbic acid can be one treatment of choices for Covid19 pneumonia [115]. A report on this disease indicates the severity. For example, a 26 % ICU admission and a 4.3 % mortality rate are observed among 138 cases [116]. It is believed that ARDS is the main mechanism for Covid19′s action. This is followed by increased oxidative stress because of the release of free radicals and cytokines. Considering this mechanism of the process, a large dose of Vit-C should play a key role in the management of Covid19. A study indicates out of 99 Covid19 patients, 17 of them developed ARDS [117]. Eleven patients passed away due to multiple organ failure [117]. This death was explained due to increased oxidative stress and cytokine generation that lead to ARDS. Like influenza, coronaviruses are pandemic viruses that injure lung drastically [118]. This viral infection generates a "storm" of cytokines that reacts with the endothelial cells of the lung. This interaction causes neutrophil infiltration and enhances oxidative stress and damages the function of the lung barrier [118]. ARDS is characterized by strong hypoxemia. This is propagated because of multiple reasons. Uncontrolled inflammation, oxidative injury, and damage to the alveolar-capillary barrier are the main reasons [119]. The severe increased oxidative stress causes pulmonary injuries: lung injury (ALI) and ARDS. ALI and ARDS are key factors responsible for substantially high morbidity and mortality [120,121]. An increase of C-reactive protein (hsCRP), an indicator of inflammation and oxidative stress is seen among Covid19 patients [122]. The transcription factor nuclear factor-erythroid-2–related factor 2 (Nrf2) is a major regulator of antioxidant response element (ARE) driven cytoprotective protein expression. It is believed that the activation of Nrf2 signaling pathways plays a crucial role in preventing cells and tissues to undergo oxidative stress.

Ascorbic acid is a key compound of the antioxidant system in cells and tissues [123]. The biological and medicinal properties of Vit-C in critical care management are documented [124]. It is now accepted that both viral and bacterial infections result in the production of excess cytokine [118]. Antioxidants should be given to control pandemics (Covid19) because of the non-availability of pathogen-specific vaccines and drugs. This is further strengthened by the fact that a large dose of IV Vit-C has shown successful clinical results in viral ARDS and influenza [125].

A report is known that a 26-year-old woman developed viral ARDS (rhinovirus and enterovirus-D68) [118]. She was admitted to ICU and was not responsive to routine treatment. She was then placed on ECMO on day 3, a high dose of IV (200 mg/kg body/24 h, 4 doses, one every 6 h) was initiated on ECMO. Amazingly, the lungs of the patients showed excellent improvement on day 2 of high dose IV Vit-C infusion. This improvement was characterized by X-ray imaging. She was then continued to improve and was discharged from the hospital, without the requirement of additional oxygen. After a month, X-ray of her lungs indicated a complete cure. A severe medical problem of influenza was treated with high dose IV Vit-C successfully [125]. A young patient was recommended to take a high dose of IV Vit-C (50,000 mg of Vit-C in 1000 ml Ringer's solution, infused over 90 min) and the condition of the patient improved notably by the next day. He was continued to take oral VC (2000 mg twice daily) [125].

The protective action of ascorbic acid is shown in [126]. A high dose IV Vit-C was used in 2009 to treat a New Zealand farmer (Primal Panacea) [127]. Vit-C was able to cut down ICU stay through an analysis of 18 clinical studies on 2004 ICU patients [128]. It was found that 17,000 mg/day IV Vit-C had shortened the ICU stay by 44 %. The use of IV Vit-C in 47 sepsis ICU cases was reported and a major reduction in death was possible [129]. Dietary antioxidants (Vit-C and sulforaphane) were helpful to manage oxidative-stress-induced acute inflammatory lung injury that requires mechanical ventilation [130]. Another antioxidant, natural curcumin has also been effective against inflammation that caused during pneumonia [131]. National Institutes of Health (NIH) states that high dose IV Vit-C (1.5 g/kd body weight) is safe for good health and without side effects [116].

4. Discussion and conclusions

Over the past century, the opinion that Vit-C can be used to treat cancer and viral infection has shown promises and controversies. There are cases where high dose Vit-C has shown benefits. In some cases, there have been no benefits. However, new knowledge regarding the pharmacokinetic properties of Vit-C, and recent preclinical studies, have revived interest in the utilization of high-dose Vit-C for cancer treatment [132–145]. Similar is the case of using IV Vit-C as antiviral, especially for the recent Covid19 [146–150]. It is believed that IV Vit-C has been particularly effective by inhibiting the production of cytokines storm due to Corvid19.

Covid19 pneumonia is an extremely rapidly developing disease with a high mortality rate. The main pathogenesis is the acute lung injury that causes ARDS and death. Antioxidants should have a role in the management of these conditions. Appropriate clinical studies and reports demonstrate that a timely administration of high dose IV Vit-C improves the outcome of Covid19 infection.

Additional studies detailing the use of IV Vit-C for the treatment of severe Covid19 infected pneumonia are definitively warranted. Covid19 may continue to happen in the future. Since the development of clinically active vaccines or antiviral drugs targeting specific diseases may take a long time to develop, the use of IV Vit-C as a universal agent for ARDS may have benefits behind Covid19. Additional clinical studies of the IV Vit-C and oral VC (such as liposomal-encapsulated VC) targeting other situations through different mechanisms are required to develop as soon as possible.

Author contributions

A.B. wrote the first draft of the manuscript. B.K.B. first revised the manuscript. Both authors further improved the manuscript.

Declaration of Competing Interest

The authors received no funding and have no conflict of interest to declare.

References

[1] C. Hunt, et al., Even small supplemental amounts of vitamin C can keep severely ill patients from dying, Int. J. Vitam. Nutr. Res. 64 (1994) 212–219.
[2] Ren Shiguang, et al., Infants with viral pneumonia treated with vitamin C had reduced mortality, Hebei Med. 4 (1978) 1–3.
[3] H. Hemilä, E. Chalker, 17,000 mg/day vitamin C given intravenously shortened intensive care unit stay by 44%, Nutrients 11 (4) (2019).
[4] I.M. Khan, et al., 200 mg of vitamin C reduced duration of severe pneumonia in children. Oxygen saturation was improved in less than one day, J. Rawalpindi Med. Coll. (JRMC) 18 (1) (2014) 55–57.
[5] C.W. Jungeblut, Inactivation of poliomyelitis virus by crystalline vitamin C (ascorbic acid), J. Exp. Med. 62 (1935) 317–321.
[6] C.W. Jungeblut, Vitamin C therapy and prophylaxis in experimental poliomyelitis, J. Exp. Med. 65 (1937) 127–146.
[7] C.W. Jungeblut, Further observations on vitamin C therapy in experimental poliomyelitis, J. Exp. Med. 66 (1937) 459–477.
[8] C.W. Jungeblut, R.R. Feiner, Vitamin C content of monkey tissues in experimental poliomyelitis, J. Exp. Med. 66 (1937) 479–491.
[9] C.W. Jungeblut, A further contribution to vitamin C therapy in experimental poliomyelitis, J. Exp. Med. 70 (1939) 315–332.
[10] F.R. Klenner, Virus pneumonia and its treatment with vitamin C, South. Med. Surg. 110 (2) (1948) 36.
[11] A.B. Kline, M.S. Eheart, Variations in the ascorbic acid requirements for saturation of nine normal young women, J. Nutr. 28 (1944) 413.
[12] N. Joliffe, Preventive and therapeutic use of vitamins, JAMA 129 (1945) 613.
[13] J.H. Crandon, C.C. Lund, D.B. Dill, Experimental human scurvy, N. Eng. J. Med. 223 (1940) 353.
[14] A.B. Baker, J.A. Noran, Changes in the central nervous system associated with encephalitis complicating pneumonia, Arch. Intern. Med. 76 (1945) 146–153.
[15] S. Krumholz, J.A. Luhan, Encephalitis associated with herpes zoster, Arch. Neur. Psych. 53 (1945) 59–67.
[16] R. Chambers, B.W. Zweifach, Intercellular cement and capillary permeability, Physiol. Rev. 27 (1947) 436–463.
[17] E.E. Hawley, J.P. Frazer, L.L. Button, D.J. Stevens, The effect of the administration of sodium bicarbonate and of ammonium chloride on the amount of ascorbic acid found in the urine, J. Nutr. 12 (1936) 215.
[18] F.R. Klenner, Significance of high daily intake of ascorbic acid in preventive medicine, J. Int. Acad. Prev. Med. 1 (1974) 45–69.
[19] F.R. Klenner, Use of vitamin C as an antibiotic, J. Appl. Nutr. 6 (1953).
[20] F.R. Klenner, Massive doses of vitamin C and the virus diseases, J. South Med. Surg. 113 (1951) 4.
[21] Shaw, et al., Acute and chronic ascorbic deficiencies in Rhesus monkeys, J. Nutr. 29 (1945) 365.
[22] F.R. Klenner, The treatment of poliomyelitis and other virus diseases with vitamin C, South Med. Surg. 111 (1949) 7.
[23] F.R. Klenner, The vitamin and massage treatment for acute poliomyelitis, South Med. Surg. 114 (1952) 8.
[24] A.B. Sabin, Vitamin C in relation to experimental poliomyelitis, J. Exp. Med. 69 (1939) 507.
[25] C.W. Jungeblut, Vitamin C therapy and prophylaxis in experimental poliomyelitis, J. Exp. Med. 65 (1937) 127.
[26] C.W. Jungeblut, Further observations on vitamin C therapy in experimental poliomyelitis, J. Exp. Med. 66 (1937) 450.
[27] E.L. Ginter, Cholesterol and vitamin C, Am. J. Clin. Nutr. 24 (1971) 1238–1245.
[28] C. Spittle, Atherosclerosis and vitamin C, Lancet II (1971) 1280–1281.
[29] E. Ginter, Effects of dietary cholesterol on vitamin C metabolism in laboratory animals, Acta Med. Acad. Sci. Hungary 27 (1970) 23–29.
[30] E. Ginter, et al., The effects of ascorbic acid on cholesterolemia in healthy subjects with seasonal deficit of vitamin C, Nutr. Metabol. 12 (1970) 76–86.
[31] G.C. Willis, An experimental study of the intimal ground substance in atherosclerosis, Can. Med. Assoc. J. 69 (1953) 17–22.
[32] J. Shafer, Ascorbic acid and atherosclerosis, Am. J. Clin. Nutr. 23 (1970) 27.
[33] A.M. Dannenburg, et al., Ascorbic acid in the treatment of chronic lead poisoning, JAMA 114 (1940) 1439–1440.
[34] J. Greenwood, Optimum vitamin C intake as a factor in the preservation of disc integrity, Med. Ann. DC 33 (1964) 6.
[35] E.D. Kyhos, et al., Large doses of ascorbic acid in treatment of vitamin C deficiencies, Arch. Int. Med. 75 (1945) 407.
[36] Cancer.gov, High-Dose Vitamin C (PDQ®)–Health Professional Version, “n.d.”. (2020) www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq.
[37] K.A. Naidu, Vitamin C in human health and disease is still a mystery? An overview, Nutr. J. 2 (2003) 7.
[38] S. Padayatty, M.G. Espey, M. Levine, Vitamin C, in: P.M. Coates, J.M. Betz, M.R. Blackman (Eds.), Encyclopedia of Dietary Supplements, 2nd ed., Informa Healthcare, New York, NY, 2010, pp. 821–831.
[39] W.J. McCormick, Cancer: a collagen disease, secondary to a nutritional deficiency, Arch. Pediatr. 76 (4) (1959) 166–171.
[40] E. Cameron, L. Pauling, The orthomolecular treatment of cancer. I. The role of ascorbic acid in host resistance, Chem. Biol. Interact. 9 (4) (1974) 273–283.
[41] E. Cameron, A. Campbell, The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer, Chem. Biol. Interact. 9 (4) (1974) 285–315.
[42] E. Cameron, L. Pauling, Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer, Proc. Natl. Acad. Sci. U. S. A. 73 (10) (1976) 3685–3689.
[43] E. Cameron, L. Pauling, Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer, Proc. Natl. Acad. Sci. U. S. A. 75 (9) (1978) 4538–4542.
[44] E.T. Creagan, C.G. Moertel, J.R. O'Fallon, et al., Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial, N. Engl. J. Med. 301 (13) (1979) 687–690.
[45] C.G. Moertel, T.R. Fleming, E.T. Creagan, et al., High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison, N. Engl. J. Med. 312 (3) (1985) 137–141.
[46] S.J. Padayatty, H. Sun, Y. Wang, et al., Vitamin C pharmacokinetics: implications for oral and intravenous use, Ann. Intern. Med. 140 (7) (2004) 533–537.
[47] L.J. Hoffer, M. Levine, S. Assouline, et al., Phase I clinical trial of i.v. ascorbic acid in advanced malignancy, Ann. Oncol. 19 (11) (2008) 1969–1974.
[48] J. Verrax, P.B. Calderon, Pharmacologic concentrations of ascorbate are achieved by parenteral administration and exhibit antitumoral effects, Free Radic. Biol. Med. 47 (1) (2009) 32–40.

[49] S.J. Padayatty, A.Y. Sun, Q. Chen, et al., Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects, PLoS One 5 (7) (2010) e11414.
[50] G.D. Campbell, M.H. Steinberg, J.D. Bower, Letter: ascorbic acid-induced hemolysis in G-6-PD deficiency, Ann. Intern. Med. 82 (6) (1975) 810.
[51] J.B. Mehta, S.B. Singhal, J.B.C. Mehta, Ascorbic-acid-induced haemolysis in G-6-PD deficiency, Lancet 336 (8720) (1990) 944.
[52] D.C. Rees, H. Kelsey, J.D. Richards, Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency, BMJ 306 (6881) (1993) 841–842.
[53] J.C. Barton, S.M. McDonnell, P.C. Adams, et al., Management of hemochromatosis. Hemochromatosis management working group, Ann. Intern. Med. 129 (11) (1998) 932–939.
[54] J.L. Welsh, B.A. Wagner, T.J. van't Erve, et al., Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial, Cancer Chemother. Pharmacol. 71 (3) (2013) 765–775.
[55] W. Zou, P. Yue, N. Lin, et al., Vitamin C inactivates the proteasome inhibitor PS-341 in human cancer cells, Clin. Cancer Res. 12 (1) (2006) 273–280.
[56] D. Llobet, N. Eritja, M. Encinas, et al., Antioxidants block proteasome inhibitor function in endometrial carcinoma cells, Anticancer Drugs 19 (2) (2008) 115–124.
[57] G. Perrone, T. Hideshima, H. Ikeda, et al., Ascorbic acid inhibits antitumor activity of bortezomib in vivo, Leukemia 23 (9) (2009) 1679–1686.
[58] B. Bannerman, L. Xu, M. Jones, et al., Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea, Cancer Chemother. Pharmacol. 68 (5) (2011) 1145–1154.
[59] M.L. Heaney, J.R. Gardner, N. Karasavvas, et al., Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs, Cancer Res. 68 (19) (2008) 8031–8038.
[60] E. Cameron, A. Campbell, T. Jack, The orthomolecular treatment of cancer. III. Reticulum cell sarcoma: double complete regression induced by high-dose ascorbic acid therapy, Chem. Biol. Interact. 11 (5) (1975) 387–393.
[61] S.J. Padayatty, H.D. Riordan, S.M. Hewitt, et al., Intravenously administered vitamin C as cancer therapy: three cases, CMAJ 174 (7) (2006) 937–942.
[62] C. Vollbracht, B. Schneider, V. Leendert, et al., Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany, In Vivo 25 (6) (2011) 983–990.
[63] C.H. Yeom, G.C. Jung, K.J. Song, Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration, J. Korean Med. Sci. 22 (1) (2007) 7–11.
[64] D.A. Monti, E. Mitchell, A.J. Bazzan, et al., Phase I evaluation of intravenous ascorbic acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer, PLoS One 7 (1) (2012) e29794.
[65] Y. Ma, J. Chapman, M. Levine, et al., High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy, Sci. Transl. Med. 6 (222) (2014) 222ra18.
[66] L.J. Hoffer, L. Robitaille, R. Zakarian, et al., High-dose intravenous vitamin C combined with cytotoxic chemotherapy in patients with advanced cancer: a phase I-II clinical trial, PLoS One 10 (4) (2015) e0120228.
[67] F. Wang, M.M. He, Z.X. Wang, et al., Phase I study of high-dose ascorbic acid with mFOLFOX6 or FOLFIRI in patients with metastatic colorectal cancer or gastric cancer, BMC Cancer 19 (1) (2019) 460.
[68] M.H. Qazilbash, R.M. Saliba, Y. Nieto, G. Parikh, M. Pelosini, F.B. Khan, R.B. Jones, C. Hosing, F. Mendoza, D.M. Weber, M. Wang, Arsenic trioxide with ascorbic acid and high-dose melphalan: results of a phase II randomized trial, Biol. Blood Marrow Transplant. 14 (12) (2008) 1401–1407.
[69] J.R. Berenson, R. Boccia, D. Siegel, M. Bozdech, A. Bessudo, E. Stadtmauer, J. Talisman Pomeroy, R. Steis, M. Flam, J. Lutzky, S. Jilani, Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study, Br. J. Haematol. 135 (2) (2006) 174–183.
[70] M. Sharma, H. Khan, P.F. Thall, R.Z. Orlowski, R.L. Bassett Jr, N. Shah, Q. Bashir, S. Parmar, M. Wang, J.J. Shah, C.M. Hosing, A randomized phase 2 trial of a preparative regimen of bortezomib, high-dose melphalan, arsenic trioxide, and ascorbic acid, Cancer 118 (9) (2012) 2507–2515.
[71] J.R. Berenson, J. Matous, R.A. Swift, et al., A phase I/II study of arsenic trioxide/bortezomib/ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma, Clin. Cancer Res. 13 (6) (2007) 1762–1768.
[72] R.A. Campbell, E. Sanchez, J.A. Steinberg, et al., Antimyeloma effects of arsenic trioxide are enhanced by melphalan, bortezomib and ascorbic acid, Br. J. Haematol. 138 (4) (2007) 467–478.
[73] M.H. Qazilbash, R.M. Saliba, Y. Nieto, et al., Arsenic trioxide with ascorbic acid and high-dose melphalan: results of a phase II randomized trial, Biol. Blood Marrow Transplant. 14 (12) (2008) 1401–1407.
[74] R.M. Abou-Jawde, J. Reed, M. Kelly, et al., Efficacy and safety results with the combination therapy of arsenic trioxide, dexamethasone, and ascorbic acid in multiple myeloma patients: a phase 2 trial, Med. Oncol. 23 (2) (2006) 263–272.
[75] J.R. Berenson, R. Boccia, D. Siegel, et al., Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study, Br. J. Haematol. 135 (2) (2006) 174–183.
[76] P.R. Subbarayan, M. Lima, B. Ardalan, Arsenic trioxide/ascorbic acid therapy in patients with refractory metastatic colorectal carcinoma: a clinical experience, Acta Oncol. 46 (4) (2007) 557–561.
[77] J.D. Schoenfeld, Z.A. Sibenaller, K.A. Mapuskar, et al., O2·- and H2O2-mediated disruption of Fe metabolism causes the differential susceptibility of NSCLC and GBM cancer cells to pharmacological ascorbate, Cancer Cell 32 (2) (2017) 268.
[78] Q. Chen, M.G. Espey, A.Y. Sun, et al., Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice, Proc. Natl. Acad. Sci. U. S. A. 105 (32) (2008) 11105–11109.
[79] A. Magrì, G. Germano, A. Lorenzato, S. Lamba, R. Chilà, M. Montone, V. Amodio, T. Ceruti, F. Sassi, S. Arena, S. Abrignani, High-dose vitamin C enhances cancer immunotherapy, Sci. Transl. Med. 12 (532) (2020).
[80] R.M.L. Colunga Biancatelli, M. Berrill, P.E. Marik, The antiviral properties of vitamin C, Expert Rev. Anti. Ther. 18 (2) (2020) 99–101.
[81] P.E. Marik, V. Khangoora, R. Rivera, et al., Hydrocortisone, vitamin C and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study, Chest 151 (2017) 1229–1238.
[82] H. Hemila, E. Chalker, Vitamin C for preventing and treating the common cold, Cochrane Database Syst. Rev. 1 (2013) CD000980.
[83] L. Pauling, The significance of the evidence about ascorbic acid and the common cold, Proc. Natl. Acad. Sci. U. S. A. 68 (1971) 2678–2681.
[84] L. Pauling, M. Rath, An orthomolecular theory of human health and disease, J. Orthomol. Med. 6 (1991) 135–138.
[85] Oudemans-van Straaten H.M., Spoelstra-de Man A.M.`, de Waard M.C., Vitamin C revisited, Crit. Care 18 (2014) 460.
[86] R. McNamara, A.M. Deane, J. Anstey, et al., Understanding the rationale for parenteral ascorbate (vitamin C) during an acute inflammatory reaction: a biochemical perspective, Crit. Care Resusc. 20 (2018) 174–179.
[87] L.A. While, C.Y. Freeman, B.D. Forrester, et al., In vitro effect of ascorbic acid on infectivity of herpesviruses and paramyxoviruses, J. Clin. Microbiol. 24 (1986) 527–531.
[88] M. Klein, The mechanism of the virucidal action of ascorbic acid, Science 101 (1945) 587–589.
[89] P.E. Marik, Hydrocortisone, ascorbic acid and thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid, Nutrients 10 (2018) 1762.
[90] P. Avci, F. Freire, A. Banvolgi, et al., Sodium ascorbate kills Candida albicans in vitro via iron-catalyzed fenton reaction: importance of oxygenation and metabolism, Future Microbiol. 11 (2016) 1535–1547.
[91] S. Uesato, Y. Kitagawa, T. Kaijima, et al., Inhibitory effects of 6-O-acylated L-ascorbic acids possessing a straight- or branched-acyl chain on epstein-barr virus activation, Cancer Lett. 166 (2001) 143–146.
[92] J. Cinatl, J. Cinatl, B. Weber, et al., In vitro inhibition of human cytomegalovirus replication in human foreskin fibroblasts and endothelial cells by ascorbic acid 2-phosphate, Antiviral Res. 27 (1995) 405–418.
[93] A.C. Carr, Vitamin C and immune function, Nutrients 9 (2017) 1211.
[94] J.M. May, F.E. Harrison, Role of vitamin C in the function of the vascular endothelium, Antioxid. Redox Signal. 19 (2013) 2068–2083.
[95] B. Leibovitz, B.V. Siegel, Ascorbic acid and the immune response, Adv. Exp. Med. Biol. 135 (1981) 1–25.
[96] S. Dey, B. Bishayi, Killing of S. aureus in murine peritoneal macrophages by ascorbic acid along with antibiotics chloramphenicol or ofloxacin: correlation with inflammation, Microb. Pathog. 115 (2018) 239–250.
[97] Y. Kim, H. Kim, S. Bae, et al., Vitamin C is an essential factor on the anti-viral immune response through the production of interferon-alpha/beta at the initial stage of influenza A virus (H3N2) infection, Immune Netw. 13 (2013) 70–74.
[98] W. Li, N. Maeda, M.A. Beck, Vitamin C deficiency increases the lung pathology of influenza virus-infected gulo-/- mice, J. Nutr. 136 (2006) 2611–2616.
[99] Y. Cai, Y.F. Li, L.P. Tang, et al., A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice, Biomed Res. Int. 2015 (2015) 675149.
[100] N. Valero, J. Mosquera, S. Alcocer, et al., Melatonin, minocycline and ascorbic acid reduce oxidative stress and viral titers and increase survival rate in experimental venezuelan equine encephalitis, Brain Res. 1622 (2015) 368–376.
[101] A. Lallement, Persistent parvovirus B19 viremia with chronic arthralgia treated with ascorbic acid: a case report, J. Med. Case Rep. 9 (2015) 1.
[102] B. Moens, D. Decanine, S.M. Menezes, et al., Ascorbic acid has superior ex vivo antiproliferative, cell death-inducing and immunomodulatory effects over IFN-alpha in HTLV-1-associated myelopathy, PLoS Negl. Trop. Dis. 6 (2012) e1729.
[103] A. Kataoka, H. Imai, S. Inayoshi, et al., Intermittent high-dose vitamin C therapy in patients with HTLV-I associated myelopathy, J. Neurol. Neurosurg. Psy. 56 (1993) 1213–1216.
[104] S. Harakeh, NF-kappa B-independent suppression of HIV expression by ascorbic acid, AIDS Res. Hum. Retroviruses 13 (1997) 235–239.
[105] B.D. Rawal, F. Bartolini, G.N. Vyas, In vitro inactivation of human immunodeficiency virus by ascorbic acid, Biologicals 23 (1995) 75–81.
[106] S. Harakeh, R.J. Jariwalla, L. Pauling, Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 7245–7249.
[107] S. Banic, Prevention of rabies by vitamin C, Nature 258 (1975) 153–154.
[108] Y.M. Hosakote, P.D. Jantzi, D.L. Esham, et al., Viral-mediated in hibition of antioxidant enzymes contributes to the pathogenesis of severe respiratory syncytial virus bronchiolitis, Am. J. Respir. Crit. Care Med. 183 (2011) 1550–1560.
[109] S.M. Castro, A. Guerrero-Plata, G. Suarez-Real, et al., Antioxidant treatment ameliorates respiratory syncytial virus-induced disease and lung inflammation, Am. J. Respir. Crit. Care Med. 174 (2006) 1361–1369.
[110] P.E. Marik, Vitamin C for the treatment of sepsis: the scientific rationale, Pharmacol. Therapeut. 189 (2018) 63–70.
[111] J.Y. Chen, C.Y. Chang, P.H. Feng, et al., Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain, Clin. J. Pain 25 (2009) 562–569.

[112] M.S. Kim, D.J. Kim, C.H. Na, et al., A study of intravenous administration of vitamin C in the treatment of acute herpetic pain and postherpetic neuralgia, Ann. Dermatol. 28 (2016) 677–683.
[113] L.E. Lansbury, Corticosteroids as adjunctive therapy in the treatment of influenza: an updated cochrane systematic review and meta-analysis, Crit. Care Med. 1 (2019), https://doi.org/10.1097/CCM.0000000000004093 ePub.
[114] C. Rodrigo, Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis, J. Infect. Dis. 212 (2015) 183–194.
[115] Orthomolecular.org, Early Large Dose Intravenous Vitamin C is the Treatment of Choice for 2019-nCov Pneumonia, (2020) orthomolecular.org/resources/omns/v16n11.shtml.
[116] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA (2020), https://doi.org/10.1001/jama.2020.1585.
[117] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.
[118] A.A. Fowler III, C. Kim, L. Lepler, R. Malhotra, O. Debesa, R. Natarajan, B.J. Fisher, A. Syed, C. DeWilde, A. Priday, V. Kasirajan, Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome, World J. Crit. Care Med. 6 (1) (2017) 85–90.
[119] L. Meng, X. Zhao, H. Zhang, HIPK1 interference attenuates inflammation and oxidative stress of acute lung injury via autophagy, Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 25 (2019) 827–835.
[120] X. Yan, X. Fu, Y. Jia, X. Ma, J. Tao, T. Yang, H. Ma, X. Liang, X. Liu, J. Yang, J. Wei, Nrf2/Keap1/ARE signaling mediated an antioxidative protection of human placental mesenchymal stem cells of fetal origin in alveolar epithelial cells, Oxid. Med. Cell. Longev. 2019 (2019) 2654910.
[121] L. Hecker, Mechanisms and consequences of oxidative stress in lung disease: therapeutic implications for an aging populace, Am. J. Physiol. Lung Cell Mol. Physiol. 314 (4) (2018) L642–653.
[122] L. Chen, H.G. Liu, W. Liu, J. Liu, K. Liu, J. Shang, Y. Deng, S. Wei, [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi Zhonghua Jiehe He Huxi Zazhi, Chin. J. Tuberc. Respir. Dis. 43 (0) (2020) E005, https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0005.
[123] Q. Liu, Y. Gao, X. Ci, Role of Nrf2 and its activators in respiratory diseases, Oxid. Med. Cell. Longev. 2019 (2019) 7090534.
[124] C.S. Nabzdyk, E.A. Bittner, Vitamin C in the critically ill - indications and controversies, World J. Crit. Care Med. 7 (5) (2018) 52–61.
[125] M.J. Gonzalez, et al., High dose vitamin C and influenza: a case report, J. Orthomol. Med. 33 (3) (2018), isom.ca/article/high-dose-vitamin-c-influenza-case-report/.
[126] V.V. Zarubaeva, A.V. Slitaa, I.N. Lavrentyevaa, V.S. Smirnovb, Protective activity of ascorbic acid at influenza infection, Russ. J. Infect. Immun. 7 (4) (2017) 319–326.
[127] T.E. Levy, Primal Panacea, MedFox Publishing, Henderson, NV, USA, 2012 350 p..
[128] H. Hemilä, E. Chalker, Vitamin C can shorten the length of stay in the ICU: a meta-analysis, Nutrients 11 (4) (2019).
[129] P.E. Marik, V. Khangoora, R. Rivera, M.H. Hooper, J. Catravas, Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study, Chest 151 (6) (2017) 1229–1238.
[130] V. Patel, K. Dial, J. Wu, A.G. Gauthier, W. Wu, M. Lin, M.G. Espey, D.D. Thomas, C.R.A. Jr, L.L. Mantell, Dietary antioxidants significantly attenuate hyperoxia-induced acute inflammatory lung injury by enhancing macrophage function via reducing the accumulation of airway HMGB1, Int. J. Mol. Sci. 21 (3) (2020).
[131] B. Zhang, S. Swamy, S. Balijepalli, S. Panicker, J. Mooliyil, M.A. Sherman, J. Parkkinen, K. Raghavendran, M.V. Suresh, Direct pulmonary delivery of solubilized curcumin reduces severity of lethal pneumonia, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 33 (12) (2019) 13294–13309.
[132] B. Ngo, J.M. Van Riper, L.C. Cantley, J. Yun, Targeting cancer vulnerabilities with high-dose vitamin C, Nat. Rev. Cancer 19 (5) (2019) 271–282.
[133] E. Ma, et al., Pharmacologic ascorbate induces neuroblastoma cell death by hydrogen peroxide mediated DNA damage and reduction in cancer cell glycolysis, Free Radic. Biol. Med. 113 (2017) 36–47.
[134] Z. Rychtarcikova, et al., Tumor-initiating cells of breast and prostate origin show alterations in the expression of genes related to iron metabolism, Oncotarget 8 (2017) 6376–6398.
[135] N. Shenoy, et al., Upregulation of TET activity with ascorbic acid induces epigenetic modulation of lymphoma cells, Blood Cancer J. 7 (2017) e587.
[136] J. Xia, et al., Multiple myeloma tumor cells are selectively killed by pharmacologically-dosed ascorbic acid, EBioMedicine 18 (2017) 41–49.
[137] Y.-X. Lu, et al., Pharmacological ascorbate suppresses growth of gastric cancer cells with GLUT1 overexpression and enhances the efficacy of oxaliplatin through redox modulation, Theranostics 8 (2018) 1312–1326.
[138] J. Quinn, et al., Effect of high-dose vitamin C infusion in a glucose-6-phosphate dehydrogenase-deficient patient, Case Rep. Med. 2017 (2017) 5202606.
[139] L. Cimmino, et al., Restoration of TET2 function blocks aberrant self-renewal and leukemia progression, Cell 170 (2017) 1079–1095.
[140] M. Mingay, et al., Vitamin C-induced epigenomic remodelling in IDH1 mutant acute myeloid leukaemia, Leukemia 32 (2018) 11–20.
[141] D. Peng, et al., Vitamin C increases 5-hydroxymethylcytosine level and inhibits the growth of bladder cancer, Clin. Epigenetics 10 (2018) 94.
[142] M. Agathocleous, et al., Ascorbate regulates haematopoietic stem cell function and leukaemogenesis, Nature 549 (2017) 476–481.
[143] J.G. Wilkes, et al., Pharmacologic ascorbate (P-AscH-) suppresses hypoxia-inducible Factor-1α (HIF-1α) in pancreatic adenocarcinoma, Clin. Exp. Metastasis 35 (2018) 37–51.
[144] C. Wohlrab, et al., The association between ascorbate and the hypoxia-inducible factors in human renal cell carcinoma requires a functional Von Hippel-Lindau protein, Front. Oncol. 8 (2018) 574.
[145] S. Mustafi, et al., Vitamin C sensitizes melanoma to BET inhibitors, Cancer Res. 78 (2018) 572–583.
[146] A. Erol, High-dose Intravenous Vitamin C Treatment for COVID-19, OSF Preprints, 2020, https://doi.org/10.31219/osf.io/p7ex8.
[147] A.S. Fauci, H.C. Lane, R.R. Redfield, Covid-19—navigating the uncharted, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMe2002387.
[148] L. Zhang, Y. Liu, Potential interventions for novel coronavirus in China: a systematic review, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25707.
[149] G. Zhang, C. Hu, L. Luo, F. Fang, Y. Chen, J. Li, Z. Peng, H. Pan, Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China, medRxiv (2020), https://doi.org/10.1101/2020.03.02.20030452.
[150] R. Qiu, X. Wei, M. Zhao, C. Zhong, C. Zhao, J. Hu, M. Li, Y. Huang, S. Han, T. He, J. Chen, Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review, medRxiv (2020), https://doi.org/10.1101/2020.03.04.20031401.