THE POTENCY OF VITAMIN C AS PREVENTION AND THERAPY AGAINST COVID-19 VITAMIN C AGAINST COVID-19: A SYSTEMATIC REVIEW

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Abstract

COVID-19 affects more than 200 countries worldwide. This viral infection leads to systemic inflammation elevation, characterized by high pro-inflammatory cytokines and oxidative damage. Vitamin C (VC) functions as an antioxidant by protecting cells from oxidative damage and suppressing the cytokine storm's phenomenon. This review highlighted the possibility of VC for prevention and management in COVID-19. This review is a scoping review; literature searching was conducted using PubMed, Clinical Key, and Google Scholar until August 2020. The keywords used were COVID-19 and vitamin C. Sixteen articles were further analyzed. The reviewed studies consist of seven case reports, three case series, three cohort studies, and three bioinformatics analyses. Some studies highlight the improvement of the COVID-19 patient's condition after VC treatment combined with other therapies. In bioinformatics studies, all studies showed the therapeutic targets for VC in COVID-19 involved in inflammation and oxidative damage pathway. The mechanisms of VC against COVID-19 are associated with oxidative damage by acting as reactive oxygen species (ROS) scavengers or depressing the ROS production and cytokine storm pathways by suppressing pro-inflammatory cytokines and apoptotic process stimulation following the neutrophil activation.

Keywords: COVID-19; vitamin C; cytokine storm; oxidative stress; antioxidant

Introduction

The severity and mortality rate in COVID-19 are affected by oxidative damage, while COVID-19 complications are associated with the cytokine storm phenomenon. An excessive amount of

reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced with antioxidants deprivation.[1-3] VC, known as ascorbate or ascorbic acid, functions as an antioxidant by protecting cells from ROS. VC is also found to aid the immune system oppose the cytokine storm phenomenon.[4] Previous studies have shown the protective properties of VC against avian coronavirus and its ability to reduce the vulnerability of pneumonia and viral respiratory infections, suggesting VC as prophylaxis and therapy for COVID-19.[5,6] Therefore, this review focused on the possibility of VC for prevention and management in COVID-19.

Materials and Methods

Literature searching was conducted using PubMed, Clinical Key, and Google scholar for articles published until August 2020. The keywords used were: "COVID-19" and "Vitamin C" using medical subject headings (MeSH) terms for a PubMed electronic database search. All citations were imported into a bibliographic database, and duplicates were removed. The inclusion criteria were articles published until August 2020, focusing on the effect of VC on prevention and management and related COVID-19. In addition, review articles, comments, protocol, ongoing trial, no full paper access, non-English articles were excluded; independently performed by two reviewers. Process and results are visualized using PRISMA-ScR[7] and described in figure 1.

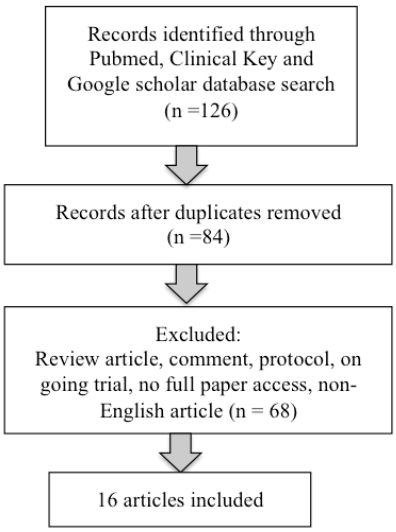

Figure 1 Flowchart describing the literature search process

Results

This research got 16 articles for further analysis. Table 1 presents all VC studies in COVID-19, consisting of seven case reports, three case series, three cohort studies, and three bioinformatics analyses.

Table 1. Studies for VC and COVID-19

No	Type of Study	Finding (related with VC)	Reff

1	Case report	Female, 74 years old (y.o), improved clinically after being treated with infusion of high-dose intravenous VC with other therapies for COVID-19.	(8)
2	Case report	Female, 77 y.o, treated with high dose intravenous ascorbic acid (1-6 gr/once or twice a day) and other therapies for COVID-19, remained critically ill (severe ARDS), and passed away.	(9)
3	Case report	Male, 61 y.o, treated with VC up to 1 g/day and other therapies for COVID-19. After 10 days of hospital treatment, the patient recovered and was discharged from the hospital.	(10)
4	Case report	Pregnant, Female, 33 y.o, VC 250 mg was administrated by gavage with other therapies for COVID-19. The maternal welfare was achieved and the neonate was discharged.	(11)
5	Case report	Male, 29 y.o, VC (dose unknown) with other therapies for COVID-19, died after being treated in hospital for 20 days.	(12)
6	Case report	Female, 62 y.o, treated with VC (orally 200 mg 3× daily) plus Diammonium glycyrrhizinate (DG) with doses 3×150 mg daily per-oral for eight days, the patient recovered.	(13)
7	Case report	Two patients: 1. Female, 57 y.o, treated in ICU with VC (3g/day) and other therapies for COVID-19. She recovered and was discharged from ICU in 14 days. 2. Male, 29 y.o, treated with VC (3g/day) and other therapies for COVID-19. He recovered and was discharged from ICU in 8 days.	(14)
8	Case series	17 patients, age mean 64±14 y.o, were treated with Intravenous (IV) VC with a median of eight days after symptom onset. The inflammatory markers were decreased significantly.	(15)
9	Case series	18 patients, age mean 59±9 y.o. The deficiency of VC level in COVID-19 patients with ARDS.	(16)
10	Case series	55 patients, age median 29 y.o (IQR, 20–44). Forty patients were treated with VC and other therapies for COVID-19. The outcome associated with VC was not clear.	(17)
11	Cohort study	152 patients, age mean 66 ± 13 y.o. This study compared COVID-19 survivors and non-survivors. The mortality risk was decreased in patients with mechanical ventilation treated with VC	(18)

12	Cohort study	596 patients, COVID-19 patients plus cardiovascular disease (CVD) compared with COVID-19 patients without CVD. VC treatment was more implicated in patients of COVID-19 with CVD.	(19)
13	Cohort study	1938 participants, 37.7% who consumed nutritional supplements (included VC), had a significantly higher Household Dietary Diversity Score (HDDS). People living in areas with rising COVID-19 confirmed cases had lower dietary diversity scores.	(20)
14	Bioinformatics Analysis	The VC's four best essential targets to combat sepsis in COVID-19 were epidermal growth factor receptor (EGFR), signal transducer, mitogen-activated protein kinase-1 (MAPK1), proto-oncogene c (JUN), and activator of transcription-3 (STAT3).	(21)
15	Bioinformatics Analysis	The VC's key target with glycyrrhizic acid (GA) treatment in combating COVID-19 was immunity activation and the anti-inflammation pathway.	(22)
16	Bioinformatics Analysis	The target pathways for a combination of VC, glycyrrhizic acid, and curcumin (VCG Plus) against COVID-19 were by regulating innate immune system through activity on Toll-like signaling and NOD-like pathways, as activator and balancer in T-cells, also depress the inflammatory responses through impeding NF-κB, MAPK, and PI3K/AKT signaling pathways.	(23)

Some studies highlight the association of VC and COVID-19. VC treatment combined with other therapies ameliorated the COVID-19 patient's condition (8, 11, 13, 14, 18, 19). In bioinformatics studies, all studies explored the mechanism against COVID-19, which involves inflammation and oxidative damage pathways. (21-23).

Discussion

The possibility of VC as one of the treatments and as a preventive agent *for COVID-19*

The cytokine storm is the major contributor to the mortality of COVID-19. The key to cytokine storm is TNF, IFN-α/ β, IFN γ, IL-1β, IL-6, chemokine (C-C motif), and ligand2 (CCL2), which promotes inflammatory responses, endothelial dysfunction, and pulmonary fibrosis.[24] Seven case reports showed leukocytosis (8, 14) and higher levels of pro-inflammatory cytokines, especially IL-6 (8, 12). In addition, most studies showed lymphopenia.[8.10-12.14] Lymphopenia in COVID-19 is due to the ability of SARS-CoV-2 to activate the p53 signaling pathway, one of the essential pathways for cell survival and apoptosis.[3]

A remarkably significant oxidative stress results from the imbalance of pro-oxidants-antioxidants in ARDS COVID-19 complication.[25] VC functions as an antioxidant by protecting cells from free radicals and has antiviral properties, which leads to reduction of inflammation and modulation of cytokines.[26] VC's requirement increases when the infection becomes more severe. The remarkably depressed VC level in COVID-19 patients with ARDS suggested the early use of VC may be an effective therapy and prophylaxis to prevent the severity of infection for COVID-19 patients.[16]

Biomolecular mechanism of VC as the treatment and preventive for COVID-19

The possible mechanisms of VC against COVID-19 are described in figure 2. The pathway for COVID-19 to induce cytokine storm involves mainly APCs. Toll-like receptor (TLR) 2 and 4 send signals for the interferon response factor 3 (IRF3) and NF-κB activation to induce the secretion of cytokines and type I interferon. TLR2 also leads to the activation of activating protein-1 (AP-1) via MAPK pathways, such as P38 and Jun N-terminal kinase (JNK). AP-1 is also responsible for the transcription of inflammatory cytokines. This mechanism will increase the secretion of pro-inflammatory cytokines, leading to cytokine storm.[3] These pro-inflammatory cytokines can stimulate the production and generation of free radicals by STAT3 and activation of NADPH oxidases1/2 (NOX1/2) complexes.[27]

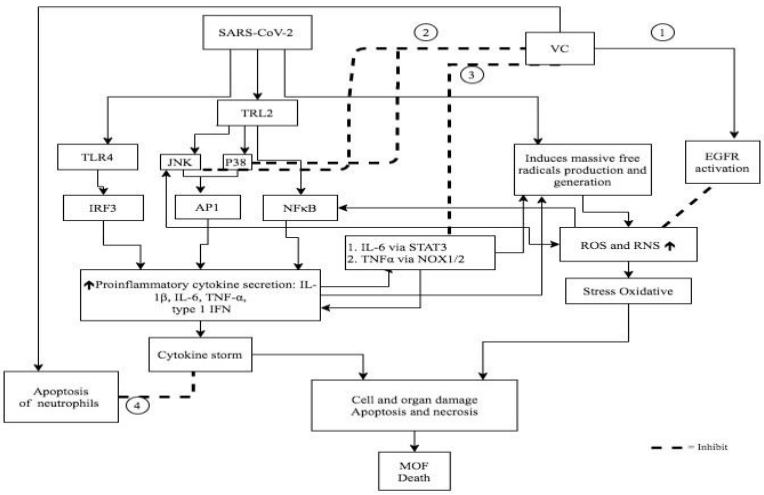

Figure 2. The possible mechanisms of VC against COVID-19

First, VC acts as a ROS scavenger through EGFR activation. Second, VC inhibits pro-inflammatory cytokines by inhibiting P38 and JUN. Third, VC decreases ROS production by inhibiting STAT. Fourth, VC stimulates the apoptotic process following the neutrophil activation. AP-1, activating protein-1; IFN, interferon; IRF3, interferon response factor 3; IL, interleukin; JNK, Jun N-terminal kinase; NFκB, Nuclear factor κ B; NOX1/2, NADPH oxidases1/2; MOF, Multi-organ failure; ROS, Reactive oxygen species; RNS: Reactive nitrogen species; STAT 3, Signal transducer and activator of transcription 3; TLR, Toll-like receptor.

Virus infection can induce massive production of free radicals.[28] Excessive free radicals will lead to oxidative damage.[2] Moreover, ROS can trigger the JNK pathway by restraining MAPK phosphatases. JNK also stimulates the production of mitochondrial ROS through mitochondrial outer membrane protein, Sab (SH3BP5) 2.[9] Combining cytokine storm and oxidative damage will lead to organ failure and death.

VC is proposed to combat COVID-19 through several possible mechanisms. First, VC as ROS scavenger via EGFR activation;[21] overexpression of EGFR in phosphorylation of eukaryotic initiation factor-2α (eIF2α) increases ROS scavenging ability and alleviates ROS-mediated cell death.[30]

Second, VC can inhibit the pro-inflammatory cytokine by inhibiting the MAPK pathway.[21] In one in-vivo study, VC pretreatment alleviated Lipopolysaccharide (LPS)-induced oxidative damage by modulating the P38-MAPK pathway.[31] Third, VC decreases ROS production via STAT 3 (21). The deficiency of VC in rats was reported to increase acute phase proteins level through IL-6 and STAT3 pathways.[32] Fourth, VC could stimulate the apoptotic process following the neutrophil activation.[33] In a whole frame of immune function, VC has many roles; raising the integrity of the epithelial barrier, enhancing neutrophil and macrophage function, as well as differentiation and proliferation of B- and T-lymphocytes to modulate cytokine production.[34] Several animals and in vitro studies in avians had been conducted to explore the protective properties of vitamin C against avian coronavirus.[35,36]

Nevertheless, more studies are needed to explore the mechanism in detail; many trials are now still going on worldwide.[37,38] The limitation of this review was that this study only reached the phase of qualitative synthesis. Therefore, further research is needed to perform quantitative analysis. Besides that, because the development of research on covid is swift, more updated reviews are required about this topic.

Conclusions

VC holds potential as adjuvant therapy and as prevention for COVID-19. Its mechanism to combat COVID-19 is associated with oxidative damage by acting as a ROS scavenger, depressing ROS production, inhibiting the cytokine storm pathways by inhibiting pro-inflammatory cytokines production, and stimulating the apoptotic process following the neutrophil activation.

Competing Interests

The authors report no conflicts of interest.

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