Review Article

nutrition and health

Nutrition and Health
1–19

DOI: 10.1177/02601060221139628
journals.sagepub.com/home/nah
SAGE

Unwinding the potentials of vitamin C in COVID-19 and other diseases: An updated review

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Abstract

Background: The discovery of vitamin C (ascorbic acid) is related to the ancient history of persistent research on the origins of the haemorrhagic disease scurvy. Vitamin C is an important nutrient that aids in a variety of biological and physiological processes. Scientists have been researching the function of vitamin C in the prevention and ailment of sepsis and pneumonia for decades. This has created a potential platform for applying these results to individuals suffering from severe coronavirus infection (COVID-19). Vitamin C's ability to activate and enhance the immune system makes it a promising treatment in the present COVID-19 pandemic. Vitamin C also aids in the activation of vitamin B, the production of certain neurotransmitters, and the transformation of cholesterol into bile acids. Hence, vitamin C is used for the treatment of many diseases. **Aim:** This review highlights the Vitamin C investigations that are performed by various researchers on patients with COVID 19 infection, the clinical studies and their observations. The authors have additionally updated information on the significance of vitamin C insufficiency, as well as its relevance and involvement in diseases such as cancer, wound healing, iron deficiency anaemia, atherosclerosis and neurodegenerative disorders. Here, we discuss them with the references. **Methods:** The method used in order to perform literature search was done using SciFinder, PubMed and ScienceDirect. **Results:** There is a potential role of vitamin C in various diseases including neurodegenerative disorders, COVID-19 and other diseases and the results are highlighted in the review with the help of clinical and preclinical data. **Conclusion:** More research on vitamin C and the undergoing clinical trials might prove a potential role of vitamin C in protecting the population from current COVID-19 pandemic.

Keywords

Vitamin C, scurvy, antioxidant, neurodegenerative, COVID-19

Introduction

Micronutrients are essential for the immune system's proper functioning and play an important part in supporting health and nutritional well-being (Cámara et al., 2021). Vitamins are necessary for the human body for several biochemical and physiological activities. Vitamins are categorised according to their solubility: (1) water soluble such as B and C complexes and (2) fat-soluble vitamins A, D, E and K (Chambial et al., 2013). Vitamin C is a water-soluble, thermolabile vitamin that is necessary for human health. Vitamin C is found in two forms in living organisms as ascorbic acid (AA)-reduced form and dehydroascorbic acid-oxidised form (Kocot et al., 2017b). The biosynthesis and catabolism of vitamin C is shown in Figures 1 and 2. Despite rising public concern over the malnutrition of micronutrients in low-income and middle-income countries which leads to bad health, greater morbidity and death rates, the worldwide status and prevalence of vitamin C deficiency has not been fully documented (Rowe and Carr, 2020). Humans like the majority of animals do not possess the enzyme L-gluconolactone oxidase which is accountable for vitamin C production, hence, enough vitamin C intake is critical (Langlois and Lamontagne, 2019). This enzyme's deficiency is the product of a mutation that happened about 40 million years ago (Nishikimi et al., 1994). Many regulatory authorities of the countries have decided to increase the recommended dose of vitamin C intake in their countries as a result of growing

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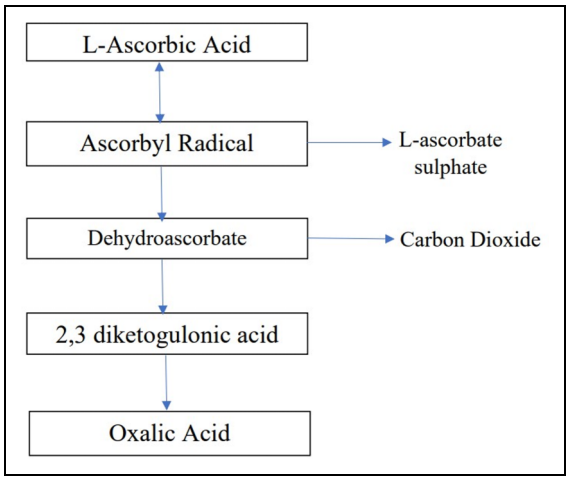

Figure 1. Catabolism of ascorbic acid.

evidence that increasing the vitamin C intake improves long-term health outcomes (Dickinson et al., 2009; Khan and Iqbal, 2006).

Vitamin C is necessary for a variety of physiological activities. It contributes to the production and metabolism of tyrosine, tryptophan and folic acid as well as the hydroxylation of proline, glycine, lysine, carnitine and catecholamines (Chambial et al., 2013). Vitamin C is a required nutrient for human life as well as a cofactor in the production of collagen (Caritá et al., 2020). It makes cholesterol conversion to bile acids easier, lowering blood cholesterol levels. Vitamin C has various applications in chronic diseases. Vitamin C is a potent antioxidant that contributes to the maintenance of good health and illness prevention. Vitamin C also helps to prevent sepsis-related coagulation problems by lowering pro-inflammatory responses, improving the function of the epithelial barrier, improving alveolar fluid clearance and reducing pro-inflammatory responses (Bharara et al., 2016). Patients who are critically ill and who are suffering from sepsis or multiple organ failure do have lower amounts of vitamin C. They require around 20 to 30 times the amount of vitamin C required by the average population (Carr et al., 2017).

The review highlights the promising role of vitamin C in various diseases such as COVID-19, central nervous system (CNS) disorder to name a few. The method adopted in order to gather information were from different search engines including SciFinder, Sciencedirect and PubMed. This different search engines were used to find out the appropriate literature regarding vitamin C, COVID-19, CNS disorders and other diseases using keywords like vitamin C deficiency, CNS disorders, cardiovascular diseases, ascorbic acid, immunity, toxicity, mechanism of action and clinical trials. The Introduction section covers the various aspects of vitamin C with citation of 15 articles. The mechanism of action and role of vitamin C in immunity covers the citation of 28 articles. The section of vitamin C and toxicity part covers the citation of 19 articles. The treatment of critically ill patients consists of citation of seven articles. The disease part unravels the role of vitamin C in various diseases contains citation of 91 articles. The nutritional strategies of vitamin C in various drug delivery systems consist of citation of five articles.

This review attempts to summarise diverse shreds of evidence in the context of therapeutic roles of vitamin C in various clinical aspects like scurvy, and CNS disorders to name a few. For example, scurvy is a syndrome, caused due to insufficiency of vitamin C for a long time defined by the weakening of the collagenous structure which leads to poor wound healing and impaired immunity (Sunil Kumar et al., 2017). Vitamin C deficiency is also reported in smokers, alcoholics as well as mentally ill patients (Lewis et al., 1998). According to research, vitamin C deficiency is linked to the development of neurological diseases such as Huntington's, Parkinson's, Alzheimer's, multiple sclerosis, and amyotrophic lateral sclerosis, as well as mental disorders like anxiety, depression and schizophrenia (Kocot et al., 2017a). Vitamin C treatment is likely to enhance outcomes in patients with COVID-19 infection, based on findings from clinical trials of people with pneumonia and sepsis, as well as preliminary observational and interventional investigations of patients with COVID-19 infection (Carr and Rowe, 2020). Globally, we observe the presence of low vitamin C in most of the common health conditions. Various studies from basic science to the clinical application of vitamin C have reported to have strong association with vitamin C in acute and chronic conditions. In this article, focus is to discuss the potentials of vitamin C in COVID-19 and many other diseases.

Mechanism of action of vitamin C

Vitamin C is a co-substrate for a variety of enzymes that are essential for the body's optimal functioning. The mechanism of action of vitamin C is depicted in Figure 3. Vitamin C is predominantly converted to its ionised form ascorbate (ASC) at physiological pH. Because of their poor hydrophobicity, ASC and dehydroascorbate (DHA) have to rely on interactions with the transporter molecules which are anchored in the cell membrane to cross biological membranes. Sodium ascorbate co-transporter 1 (SVCT1) and SVCT2, both are the glycoproteins that are responsible for the transportation of ASC into the cell, which are recognised as SVCTs (Daruwala et al., 1999). SVCT1 is only present within epithelial cells where the amount of ASC transported is more than that of the amount which is required by the cells (Liang et al., 2001). Enterocytes can take up ASC and DHA via the SVCT and glucose transporters (GLUTs), respectively (Malo and Wilson, 2000). Although they have different cellular sites, enterocytes express GLUT1, GLUT2 and GLUT3 (Harris et al., 1992; Helliwell et al., 2000; Mesonero et al., 1994). The apical brush-border membrane contains GLUT3, while the basolateral membrane has GLUT1 and GLUT2 which are

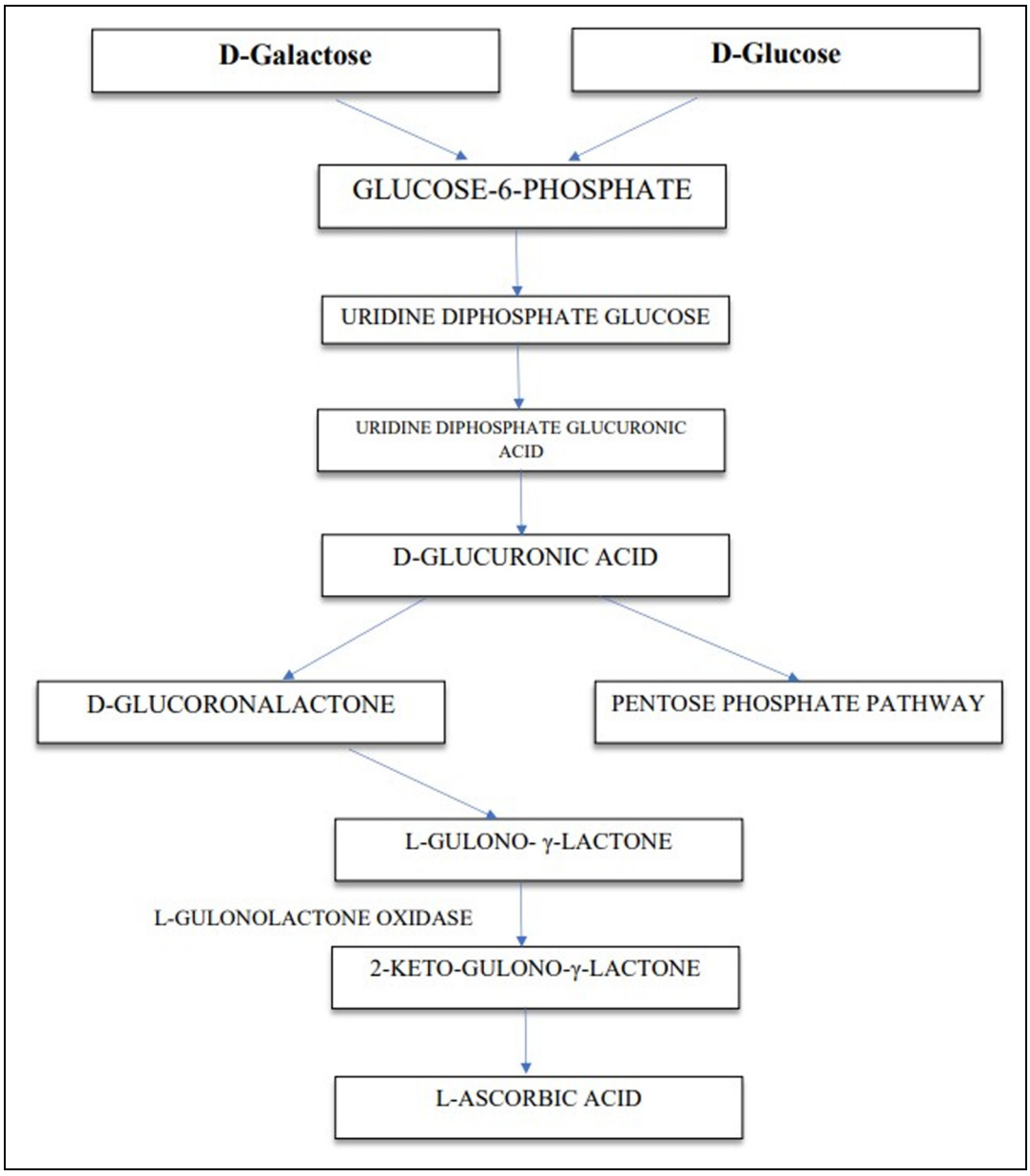

Figure 2. Biosynthesis of L-ascorbic acid in animals.

located on both sides of the membrane. Vitamin C is thought to enter the bloodstream via endothelial discontinuities and circulate with the blood throughout the body, where it is usually identified as the ASC anion (Wilson, 2005). Both ASC, as well as DHA, are absorbed through the length of the small intestine (duodenum, jejunum and ileum) (Malo and Wilson, 2000; Mellors et al., 1977; Stevenson, 1974). ASC is absorbed differently than glucose, with ASC being faster absorbed in almost the distal segments of the small intestine and absorbed in lesser amounts in proximal portions. The jejunum absorbs DHA better, while the ileum's distal parts absorb only a small quantity (Malo and Wilson, 2000). Several glucose transporters have showed that DHA competes with glucose for transfer (Corpe et al., 2013; Vera et al., 1993). DHA is transported by facilitated diffusion, which allows it to travel along the concentration gradient. DHA is converted to ASC as soon as it crosses through the membrane, therefore, this gradient is maintained (Asard et al., 2005; Hughes and Maton, 1968; Rumsey et al., 2000; Washko et al., 1993). It was established that vitamin C transport is satiable, concentration, energy, temperature, as well as dependent on sodium and is mediated by two distinct components. The blood–brain barrier prevents ASC from entering the brain because it is not permeable to ASC and lacking the SVCT2 expression (Agus et al., 1997; García et al., 2005; Qiao and May, 2008). On the other hand due to the expression of GLUT1, DHA easily passes through the blood–brain barrier (Agus et al., 1997; Farrell et al., 1992). Renal glomeruli filters and remove

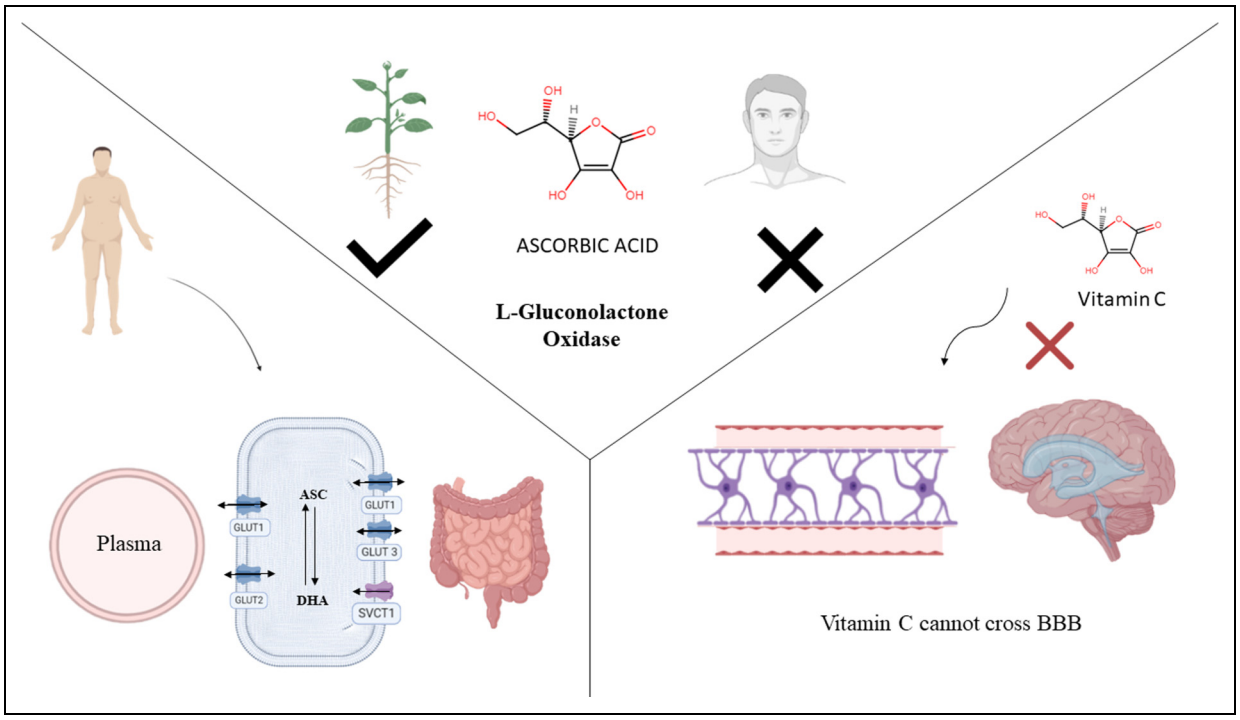

Figure 3. (a) Humans cannot synthesise vitamin C due to lack of L-gluconolactone oxidase enzyme. Plants can synthesise ascorbate due to presence of L-gluconolactone oxidase enzyme. (b) Mechanism of action of vitamin C and (c) ascorbate molecule is impermeable to blood–brain barrier and lacks SVCT2 expression. ASC: ascorbate; DHA: dehydroascorbate; GLUT: glucose transporter; SVCT: sodium ascorbate co-transporter.

ASC from the blood and excrete it into the urine (Friedman et al., 1940). Consequently, a considerable part of vitamin C is being reabsorbed throughout proximal tubules, depending on the individual's vitamin C status (Bowers-Komro and McCormick, 1991; Rose, 1986).

Role of vitamin C in immunity

The immune system is made up of a complex network of specialised cells, tissues, organs, proteins and chemicals that protect the host from foreign pathogens (Kellie and Al-Mansour, 2017). It is separated into epithelial barriers, as well as cellular and humoral components of innate (non-specific) and acquired (specific immunity) (Kellie and Al-Mansour, 2017). For more than a half century of study and research, vitamin C has been proven to be crucial in various areas of the immune system, most notably immune cell activity. Vitamin C is a water-soluble antioxidant found in extracellular fluid and cell cytoplasm, where it performs a variety of functions, including immune homoeostasis (De la Fuente et al., 2020). As it is quickly utilised during the defensive activities, there is high concentration of vitamin C in leukocytes which gets decreased during infections and stress. Vitamin C supplementation in the form of diet or gram doses has been demonstrated to improve neutrophil chemotactic capacity in healthy volunteers (Bozonet et al., 2015). In another study, the intake of diet rich with vitamin C, vitamin E and others showed improvement in the peritoneal leukocyte activities, restoring their redox equilibrium, and extended the life span of the animals in prematurely aged mice (Alvarado et al., 2006). Vitamin C's anti-histamine impact, according to Johnston et al. (1992), is linked to increased chemotaxis. After phagocytosis and microbial annihilation, neutrophils go into a process called cell apoptosis, which involves planned cell death. This procedure aids macrophages in phagocytosis and evacuation of dead neutrophils from inflammatory sites, allowing inflammation to be resolved faster and tissue damage to be reduced. Vitamin C is thought to prevent the oxidant-sensitive caspase-dependent apoptotic pathway after neutrophil activation. In vitro, macrophages did not phagocyte these vitamin C-deficient neutrophils, and they remained in inflammatory sites in vivo. Furthermore, giving vitamin C to sick animals leads to decrease in the amount of neutrophils in the lungs (Vissers and Wilkie, 2007).

Vitamin C deficiency

Because of random genetic alterations that happened throughout evolution, humans had lost their capacity to generate ASC in their livers (Nishikimi and Yagi, 1991). The polymorphism of single nucleotide in the SLC23A1 and SLC23A2 genes, which have been associated to human illnesses, are used to study the impact of genetic variants on vitamin C pharmacokinetics (Granger and Eck, 2018; Padayatty and Levine, 2016). Reduced renal

reabsorption was determined to be the strongest proof for numerous common single nucleotide polymorphisms (SNPs) of SLC23A1 lowering circulating vitamin C levels (Corpe et al., 2010; Michels et al., 2013; Monteiro-grillo, 1990). Crohn's disease (Amir Shaghaghi et al., 2014), non-Hodgkin lymphoma (Skibola et al., 2008), pre-term birth (Erichsen et al., 2006) and severe periodontitis (De Jong et al., 2014) all have been linked to SLC23A1 polymorphisms. Sodium-dependent transporter 1 (SVCT-1) is the primary regulator of vitamin C absorption, and it is quickly saturated, resulting in low vitamin C absorption per meal (Savini et al., 2008). More vitamin C is lost when AA gets converted to dehydroascorbic acid, which can then be later converted to AA or undergoes further oxidative breakdown (Washko et al., 1993). Several studies have revealed the relationship between the lifestyle-related diseases as well as vitamin C deficiency. In animal research, vitamin C deprivation is linked to reduced brain growth and hippocampal function. The recommended dietary allowance of vitamin C is depicted in Table 1.

Toxicity

There are several complaints for vitamin C when it is consumed in high doses, such as diarrhoea and intestinal distension or gas (Ohno et al., 2009). Vitamin C at large levels has also been proven to have the following outcomes; for increase in calcium, iron and manganese urinary excretion (Ohno et al., 2009); to enhance iron absorption; to enhance urinary oxalate or uric acid levels, for a small segment of population; and to change the several standard laboratory values. In individuals with the no prior symptoms or indications of renal impairment, evidence shows that the intravenous vitamin C is unlikely to cause any type of damage (Casciari et al., 2005). The people who are suffering from glucose-6-phosphate insufficiency, the administration of vitamin C intravenously or high oral dose of vitamin C can be a cause of haemolysis (Levine et al., 1999). According to Campell and Jack, one patient died from significant tumour necrosis and haemorrhaging followed by the initial dose of the ASC (intravenous). As a result, it is recommended that treatment should begin with the modest dose and be administered via a gradual drip infusion (Campbell and Jack, 1979). It's important to remember that, when taken in large dosages, vitamin C is a drug with adverse effects, just like any other. In the human body, vitamin C is partially converted to oxalate (Hellman and Burns, 1958). As per Figure 4, vitamin C elevates oxalate levels in urine in a dose-dependent manner, raising concerns about its safety and urinary stone development is a possibility. In the setting of hyperoxaluria, there could be the supersaturation of calcium oxalate which will be resulting in the formation of crystal nuclei in the urine. The crystals can pass swiftly in the healthy individuals but intratubular retention is thought to occur in areas of injured and tubular epithelium that regenerates, it is where the molecules with potential binding capacity of crystal are expressed (Cossey et al., 2013; Verkoelen and Verhulst, 2007). Patients who are suffering from sepsis, higher dose of vitamin C may be beneficial, so there should be a careful risk–benefit analysis of its extended administration in patients who are suffering from COVID-19 as well as kidney dysfunction and it should be carried on case-to-case basis (Fontana et al., 2020).

Table 1. RDAs of vitamin C.

Category	RDA per day
Infants (underage of 6 months)	40 mg
Infants (underage of 12 months)	50 mg
Children (underage of 8 years)	25 mg
Children (underage of 13 years)	45 mg
Male(13–17 years)	75 mg
Female(13–17 years)	65 mg
Adult male	90 mg
Adult female	75 mg
Pregnant women	85 mg
Lactating women	120 mg
Smokers	Requires 35 mg/day more vitamin C as compared to non-smokers

RDA: recommended dietary allowance.

Treatment of critically ill patients

The patients who are critically ill, vitamin C insufficiency is prevalent in them, and patients with septic shock having the lowest levels. This is most likely due to the higher metabolism caused along by septic shock's heightened inflammatory response (Carr et al., 2017). The plasma levels of vitamin C regularly play with the scurvy levels in conditions like sepsis, trauma, after major surgery and burn patients, and in any situation caused or characterised by severe systemic oxidative and inflammatory stress (Carr et al., 2017). The increased oxidative stress which is produced by the during critical illness increases antioxidant consumption and decreases antioxidant recycling, especially vitamin C. While other species boost their vitamin C production in response to stress, humans are not able to enhance the serum levels like other stress hormones. So due to this, the insufficiency exists (Langlois and Lamontagne, 2019). Administration of high-dose intravenous (IV) AA reduces demand for fluid, there is occurrence of wound oedema and weight gain in the initial phase of burn injury while simultaneously improving renal and lung function (Tanaka et al., 2000). Patients in the intensive care unit (ICU) are frequently given enteral nutrition or parenteral nutrition if they cannot get enough enteral nutrition (Yamazaki et al., 2011). The presence or lack of a working intestine, as well as the patient's haemodynamic condition, dictate the route of feeding for the patient – enteral or parenteral (Chan et al., 1999) In the case of patient having fluid restriction and organ failure, nutritional requirements are

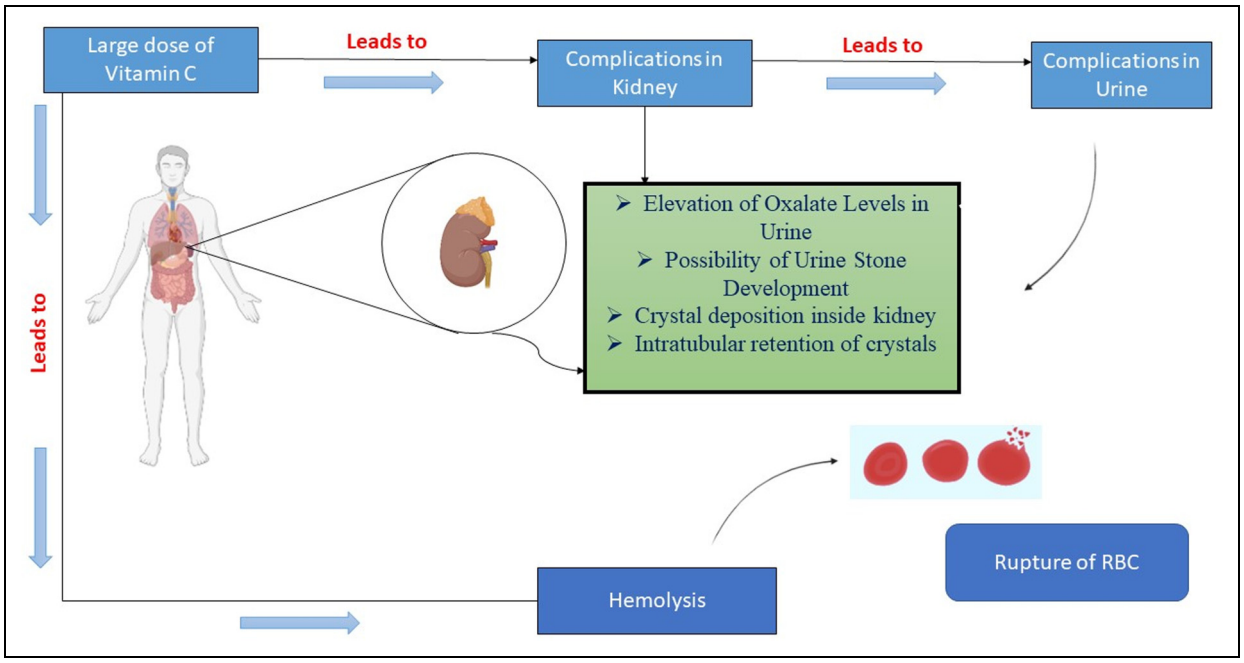

Figure 4. Toxicity of vitamin C.

usually altered (Chan et al., 1999). Enteral and parenteral nutrition, which provide 100 to 200 mg of vitamin C per day on average, are insufficient for critically ill patients. A regular intake of vitamin C of at least 2 to 3 g is likely to be required for these patients (Carr et al., 2017).

The effects of AA supplementation were first discovered in a number of animal models of sepsis and ischaemia reperfusion. The therapy of AA in a sepsis murine model was responsible for enhanced microvascular perfusion, improved blood flow and blood pressure with dosages ranging from 10 to 200 mg/kg provided either as a preventative measure or after an injury (Secor et al., 2010; Tyml et al., 2008). In septic mice, the AA infusion was responsible for enhancing the blood flow of capillary, the barrier function of microvascular and arteriolar response to vasoconstrictors (Armour et al., 2001; Wu et al., 2004). So, the supplementation of vitamin C is useful for the critically ill patients. One study revealed that despite receiving conventional ICU nutritional care, approximately 70% of the critically ill patients were suffering from hypovitaminosis C, with a substantial percentage of patients having the vitamin C insufficiency (32%). Patients suffering with septic shock cause further vitamin C depletion in the blood, with approximately 90% of patients having hypovitaminosis C and 40% having hypovitaminosis B. Vitamin C deficiency is likely due to increased inflammatory pathway activation in response to infection, as demonstrated by higher C-reactive protein levels in these patients (Carr et al., 2017).

Diseases

The role of vitamin C in various diseases is depicted in Figure 5.

COVID-19

COVID-19 is been reported as one of the most serious public health threats (Zhang et al., 2021). This outbreak began with an animal to human transmission, and severe atypical pneumonia was the immediate cause of mortality (Muscogiuri et al., 2020). The COVID-19 pandemic has caused widespread alarm and action, posing a significant risk to public health. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19 results in common cold and has main impact on the respiratory tract and human immune system (Callender et al., 2020). Patients who are aged as well as those with pre-existing respiratory, cardiac or diabetic disease seems to be at a greater risk of rapidly progressing to the severe and critical stages (Weiss and Murdoch, 2020). The search for a coronavirus-specific drug has led to a dead end, with most of the studied medications, including corticosteroids, appearing to be beneficial to patients in addition to normal therapy. Despite the encouraging published results, the vaccination process is taking its time. As a result, there is a pressing need to explore new avenues for potential treatments. When considering the possible function of vitamin C against the novel coronavirus, there are various animal studies that are relevant (Hemilä, 2017). The clinical trials data of vitamin C in COVID-19 is given in Table 2. Vitamin C aids in the downregulation of cytokines, protects the endothelium from oxidative stress, and has significant role in tissue healing, which is especially crucial during COVID-19's critical phase (Holford et al., 2020). Vitamin C also prevents the production of inflammatory cytokines. An immunological hyperreaction, involving Interleukin-6 (IL-6) and endothelin-1, appears to be driving the progression of COVID-19

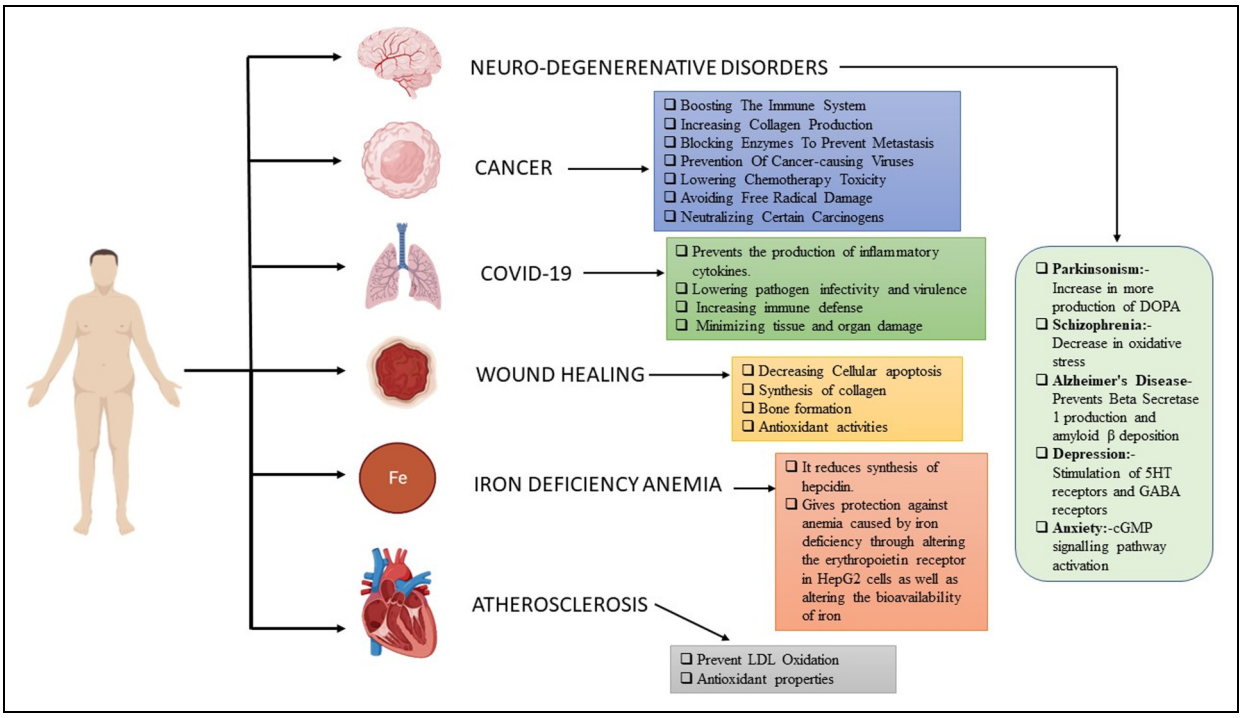

Figure 5. Various pathways and mechanism through which vitamin C acts in various diseases. 5HT: 5-hydroxytryptamine; cGMP: cyclic guanosine monophosphate; DOPA: dihydroxyphenylalanine; GABA: gamma amino butyric acid; LDL: low-density lipoprotein.

pneumonia to respiratory failure. Patients infected with COVID-19 should benefit from vitamin C, as vitamin C has been given the importance of IL-6 in severe COVID-19 and vitamin C's capacity to prevent IL-6 from increasing in a variety of (pro)inflammatory disorders (Mrityunjaya et al., 2020). Vitamin C has long been thought to help sepsis patients retain normal lung function by improving broncho-alveolar function, alveolar fluid clearance, and reduction of neutrophil sequestration. A higher amount of IV vitamin C (10–20 g/day) was successfully administered in 50 patients with severe COVID-19 infection in a recent Chinese study, and the oxygenation index was stabilised, and all of the patients were cured and discharged after a defined length of time (Farjana et al., 2020). Vitamin C studies delayed and eased upper respiratory tract infections that occurred over the course of vitamin C treatment, according to a meta-analysis of 29 randomised trials including 11,306 patients (Hemilä and Chalker, 2020). In addition, studies have shown that combining antiviral, antioxidant and immunomodulatory effects of vitamin C and quercetin are synergistic. As a result, incorporating vitamin C into a dietary supplement can aid to relax and boost the immune system while also acting as an anti-inflammatory and antioxidant against COVID-19 infection (Colunga Biancatelli et al., 2020a). High-dose vitamin C treatment can help patients with viral pneumonia and acute respiratory distress syndrome who have a severe COVID-19 infection by lowering inflammation and pathogen infectivity and virulence, increasing immune defence, minimising tissue and organ damage, and improving overall prognosis (Wessels et al., 2020). Supplementing with vitamin C can drastically minimise the need for corticosteroids, antibiotics and antiviral medications. Vitamin C enhances the innate immune response, which aids in the prevention of viral infections.

Mechanism of action of vitamin C in COVID-19. With reference to COVID-19, vitamin C has various roles including downregulation of cytokines, endothelium protection from oxidative stress as well as a critical role in tissue repair (May and Harrison, 2013; May and Qu, 2011). The oxidative stress and genes critical to the inflammatory response including IL-1, IL-8, tumour necrosis factor alpha, as well as intercellular adhesion molecule 1 is mediated through the nuclear factor kappa B (NF-κB) pathway activation (Sen and Packer, 1996). Vitamin C causes reduction in the oxidative stress as well as inflammation through activation of NF-κB pathway (Chen et al., 2014). In COVID-19, there is downregulation of interferon type 1 expression (Blanco-Melo et al., 2020). Vitamin C is responsible to upregulate the expression of these important enzymes which acts as a defence against the infection (Colunga Biancatelli et al., 2020b). The concentration of vitamin C is much higher in adrenal glands than in other body organs. Vitamin C is released from the adrenal glands in response to stress and increasing the plasma level of vitamin C (Padayatty et al., 2007). Vitamin C is also responsible for the cortisol production which eventually increases the anti-inflammatory response and cytoprotective effects of glucocorticoids (Barabutis et al., 2017; Kodama et al., 1994).

Table 2. List of clinical trials for intervention of vitamin C in COVID-19 infections.

Serial number	Title	Country	Participants	Interventions	NCT number	Status
1	Coronavirus 2019 (COVID-19) – using ascorbic acid and zinc supplementation (COVID A to Z)	The United States	214	Ascorbic acid and zinc gluconate	NCT04342728	Completed
2	Administration of intravenous vitamin C in novel coronavirus infection (COVID-19) and decreased oxygenation (AVoCaDO)	The United States	20	50 mg/kg L-ascorbic acid of infusion given every 6 h for 4 days (16 total doses)	NCT04357782	Completed
3	High-dose vitamin C treatment in critically ill patients with COVID-19	Turkey	78	The daily administration of 6 g of vitamin C intravenously in 4 equal doses every 6 h	NCT04710329	Completed
4	Lessening organ dysfunction with vitamin – COVID-19 (lovit-covid)	Canada	800	Vitamin C Control: saline or 5% dextrose solution	NCT04401150	Recruiting
5	The effect of melatonin and vitamin C on COVID-19	The United States	150	(1) 10 mg melatonin, at bedtime (2) 1000 mg vitamin C, at bedtime Placebo at bedtime	NCT04530539	Recruiting
6	The study of quadruple therapy zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19	Saudi Arabia	60	1) Zinc:50 mg 2) Quercetin:500 mg 3) Bromelin:500 mg Vitamin C:1000 mg	NCT04468139	Recruiting
7	Use of ascorbic acid in patients with COVID-19	Italy	500	10 g* of vitamin C intravenously in addition to conventional therapy	NCT04323514	Recruiting
8	Safety study of early infusion of vitamin C for the treatment of novel coronavirus acute lung injury (SAVE EVICT CORONA-ALI)	The United States	60	50 mg/kg intravenous vitamin C infusion every 6 h for up to 96 h	NCT04344184	Recruiting
9	A study of hydroxychloroquine, vitamin C, vitamin D and zinc for the prevention of COVID-19 (HELPCOVID19)	The United States	600	Experimental: hydroxychloroquine, vitamin C, vitamin D, zinc Placebo: vitamin C, vitamin D, zinc	NCT04335084	Recruiting
10	Role of mega dose of vitamin C in critical patients with COVID-19 infection	Pakistan	15	Experimental: the dose was 30 g a day (10 g TDS) for 2 days with standard treatment Placebo: distilled water in the same dose with same standard treatment	NCT04682574	Recruiting
11	International alliance study of therapies to prevent progression of COVID-19	Australia	200	Vitamin C, Hydroxychloroquine Azithromycin Zinc citrate Vitamin D3, vitamin B12	NCT04395768	Recruiting
12	Vitamin C infusion for the treatment of severe 2019-ncov-infected pneumonia	China	56	Experimental: 12g vitamin C was infused in the experimental group twice a day for 7 days Placebo: 50 ml sterile water for injection will be infused in the placebo comparator group twice a day for 7 days	NCT04264533	Terminated

NCT: National Clinical Trial number.

Clinical trials and nutritional status of vitamin C in COVID-19. The main reason responsible for lung injury in people suffering from COVID-19 is the oxidative stress and the free radicals which are generated by the immune system of the body. The antioxidant status of the patients can be improved by administration of vitamin C ("The Financial Express," 2020). There are number of studies conducted preclinically on animals which has provided the benefits and proved the efficiency of vitamin C in order to treat infections (Hemilä, 2017). A pilot study was conducted on critically ill patients suffering from sepsis. The patients were administered with IV vitamin C (50 and 200 mg/kg). The results showed that the patients administered with IV vitamin C had lower levels of pro-inflammatory markers and lower scores of Sequential Organ Failure Assessment as compared to the patients administered with placebo (Fowler et al., 2014). Another study titled 'COVID A to Z' showed a statistically significant difference in the recovery rate between the vitamin C and usual care arms (P value = 0.025). The time to reduce the symptoms by 50% was 1.2 days less in vitamin C arm in comparison with the usual arm (Hemilä et al., 2021). There are various other studies which do highlight the combination of vitamin C, hydrocortisone and thiamine which had efficient and fruitful results in sepsis (Fujii et al., 2020). There are number of clinical trials that have been announced since the start of the COVID-19 pandemic, so that the vitamin C's therapeutic benefits can be evaluated. The clinical trials are registered under National Institute of Health Clinical Trials in order to evaluate the efficiency of vitamin C in COVID-19 as alone treatment or in combination with other supplements. The randomised controlled trial was conducted in patients suffering from septic shock and the results were compared with the combination of vitamin C (6 g/day), hydrocortisone (200 mg/day) and thiamine (400 mg/day) to hydrocortisone alone. The results revealed that the combination therapy did not affect the duration of the attack but it decreases the Sequential Organ Failure Assessment scores (Fujii et al., 2020). This signifies that vitamin C has a major role in prevention and management of COVID-19. The dose of vitamin C for healthy individuals is 200 mg/day. There is increase in the requirement of dose during infections, that is, 1 to 2 g/day (Abobaker et al., 2020). The clinical trials ongoing may provide clear picture as well as evidence for the role of vitamin C in COVID-19.

Central nervous system

Vitamin C is useful for treatment of wide range of neurological and mental diseases as an adjuvant. High quantities of unsaturated fatty acids and a rapid rate of cell metabolism make the brain a particularly sensitive organ to oxidative stress and free radical activity. As an antioxidant, AA functions by scavenging reactive oxygen and nitrogen species produced during normal cell metabolism. As per Figure 6, vitamin C participates in CNS signal transduction via neurotransmitters, which is a non-antioxidant action. Vitamin C is hypothesised to play a part in this process by affecting neurotransmitter binding to receptors and controlling their release. Furthermore, several neurotransmitters, including

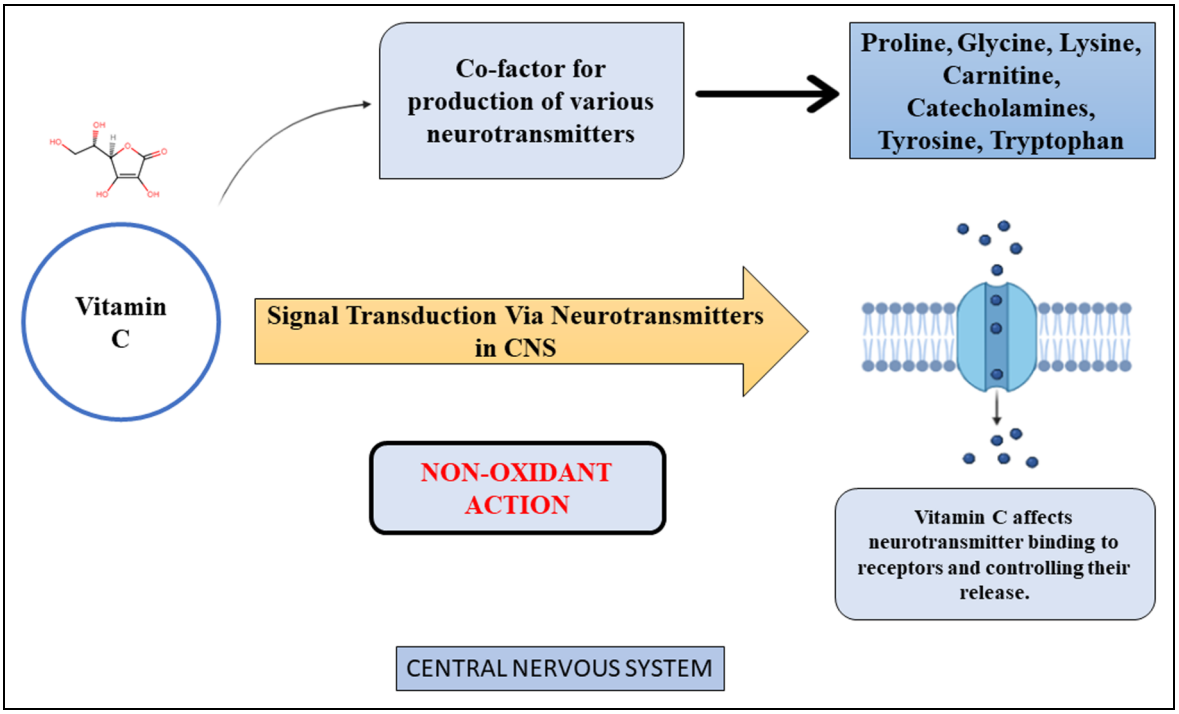

Figure 6. Non-oxidant action of vitamin C in central nervous system (CNS).

catecholamines, require vitamin C as a cofactor in their production.

Anxiety. Anxiety is a natural response that detects and prepares a person for an actual or possible threat (McNaughton and Corr, 2004). Glutamate is an excitatory neurotransmitter that plays a role in anxiety-related behaviour modulation. An elevation in glutamate signalling in the brain is linked to anxious behaviour, whereas a decrease in glutamate signalling reduces anxiety-related behaviour (Swanson et al., 2005). Patients who suffer from anxious types of depression seem to be more prone to experience depression symptoms that are severe, such as exhaustion, guilt and feelings of worthlessness (Goldberg et al., 2014). Furthermore, at a physiological level, AA shields neuronal cells against glutamate-induced excitotoxicity. The importance of internal dietary AA levels for mental wellness is critical. Dianae B. Fraga reported that in diverse animal models of anxiety, the single dose's effects of diazepam (positive control), AA or ketamine, were studied. Mice were given ketamine, AA or diazepam before mice being tested in the open field test, elevated plus maze test, marble burying test and light–dark preference test (Fraga et al., 2018). The anxiogenic and anxiolytic effects of various medications are commonly assessed using the light–dark test (Bourin and Hascoët, 2003; Gallo et al., 2014). The hypothesis behind this study is that mice avoid brightly lit surroundings and engage in spontaneously exploratory action in relation to mild stressors such as novelty and light. In the light–dark preference test, in the light region vitamin C increased latency time and duration, but had no influence on mice's performance in the marble burying test. The findings imply that AA combined with ketamine may have an anxiolytic effect, opening up a new therapy option for anxiety disorders (Fraga et al., 2018). Through cyclic guanosine monophosphate (cGMP)-mediated signalling, nitric oxide (NO) has also been shown to behave as a post-synaptic or pre-synaptic retro-grade messenger (Wang et al., 2005). The phosphorylation of synaptophysin, the protein that induces glutamate release by fusing glutamate-containing granules to the membrane of pre-synaptic nerve terminals, activates the cGMP-dependent protein kinase G pathway (Wang et al., 2005). According to Vaibhav et al., AA, an NO signalling pathway and N-methyl-D-aspartic acid receptor modulator, resulted in an anxiolytic effect in mice. When mice were administered with AA, the amount of nitrite in their brains was reduced. Anxiogenic reactions were generated by pre-treatment with NO donor and sildenafil which were followed by AA treatments (Walia et al., 2019). As a result, modulation of NO signalling was implicated in the action of AA as an anxiolytic in mice. An inherent vitamin C deficiency in SMP30/GNL knockout mice resulted in anxiety and anorexia, according to Koizumi et al. (2016).

Depression. According to World Health Organization, there are millions of people worldwide who are affected by depression. Dopamine, noradrenaline and serotonin neurotransmission disturbances may all play an important role in the illness. Depression is defined by loss of interest and persistent sorrow in the activities you enjoy the most, in addition, for at least 2 weeks, you will be unable to carry out daily activities. In addition, those who suffer from depression are likely to have multiple symptoms such as: loss of energy; changes in the appetite; change of sleeping pattern; worry; poor focus; lack of direction; restlessness; thoughts of worthlessness, regret or hopelessness; a feeling of unworthy, remorse and thoughts of suicide and self-harm (Estimates, 2014). Long-term treatment with a multivitamin that included enough vitamin C enhanced mood in persons with low plasma vitamin C levels (Helmeste and Tang, 1998). Exhaustion and psychosomatic idiosyncrasy can result from a vitamin C deficit (Vahdat Shariatpanaahi et al., 2007). The stimulation of 5-hydroxytryptamine 1A (5-HT1A) and 5-HT2A/2C receptors at post-synaptic sites has also been connected to AA's antidepressant-like activity (Binfaré et al., 2009). Furthermore, a 3-month AA treatment promoted remission of depression symptoms in 50 depressive patients who were experiencing acute depression. Amr et al. (2013) and co-workers hypothesised that AA's antidepressant activity benefits are unrelated to its antioxidant characteristics. Furthermore, investigations have shown that depressed patients have reduced levels of inhibitory neurotransmitter amino butyric acid in their brains, as well as changes in the subunit makeup of its major receptor (gamma amino butyric acid (GABA)-A) (Luscher et al., 2011). Preclinical evidence suggests that current depression medication may help to compensate for GABAnergic deficits (Luscher et al., 2011). AA's antidepressant-like effect may be due to GABA-A receptor activation and maybe the GABA-B receptor inhibition (Rosa et al., 2016). When taken with AA at a sub-effective dose, muscimol (GABA-A agonist) produced an antidepressant-like synergistic effect, but baclofen (GABA-B agonist) reduced AA's antidepressant-like effect (Rosa et al., 2016). Another study conducted in New Zealand in young adult males also suggested the possible relation with the vitamin C status as well as the mood state. The study is cross-sectional, and evidence of causality will require further well-conducted intervention studies. There are several physiological reasons for vitamin C's good influence on mood, including its role in brain function and homoeostasis (Pullar et al., 2018). Antioxidant vitamin intake, according to one study, could be a good dietary choice for preventing depression and anxiety disorders (Farhadnejad et al., 2020).

Parkinsonism. Parkinsonism is a neurodegenerative disease which is marked by tremor, stiffness and bradykinesia in the muscles. Oxidative stress is assumed being the cause of neurodegenerative diseases like Parkinsonism (Niedzielska et al., 2016). Furthermore, this ailment is hyposmia, sleep problems and depression are all linked to non-motor symptoms (Massano and Bhatia, 2012; Schapira et al., 2017). Parkinsonism is marked by the degeneration of dopaminergic neurons in substantia nigra and formation of Lewy bodies within the brain (DeMaagd and Philip, 2015). In investigations

on humans, vitamin C deficiency has already been linked with Parkinson's disease (Medeiros et al., 2016; Quiroga et al., 2014; Senarath Yapa, 1992). Vitamin C has been studied extensively in a variety of Parkinson's disease in vivo and in vitro models, and it has been shown to have beneficial effects (Kocot et al., 2017b). The *Drosophila* model was utilised by Huynh Man Anh et al. to study the duration and dose-dependent effects of vitamin C therapy on Parkinsonism symptoms caused by the knockdown of *Drosophila* ubiquitin C-terminal hydrolase. In this model, they discovered that vitamin C was found to improve Parkinsonism-like characteristics, which are characterised by neurodegeneration as well as locomotive abnormalities (Man Anh et al., 2019). On the contrary, high dose of AA had deleterious impacts on eating behaviour and motor capacity. Long-term vitamin C medication, for example, may protect against dopaminergic neuron degeneration. Vitamin C can boost dihydroxyphenylalanine synthesis (DOPA). Seitz et al. discovered that incubating the cell line of human neuroblastoma with AA resulted in more production of DOPA in dose-dependent manner. Furthermore, after treatments with AA, tyrosine hydroxylase gene expression increased thrice (Seitz et al., 1998).

Alzheimer's disease. Vitamin C insufficiency has been linked to the neuropathology of Alzheimer's disease as well as normal aging. The neuropathology of Alzheimer's disease is characterised by oxidative stress (Praticò et al., 2002; Praticò and Sung, 2004). In neurodegeneration, disturbance of AA homoeostasis has been well-documented (Covarrubias-Pinto et al., 2015). In the CNS, AA is an important antioxidant that is produced by glial cells within the synaptic cleft and then as an antioxidant defence, neurons absorb it to keep synaptic function as well as neuronal metabolism and in check. The astrocytes and neurons interaction has been discovered to be a key mechanism for AA recycling, as well as a participant in the brain's antioxidative defence (Dringen et al., 1999). Parenteral administration of AA has nootropic characteristics in amyloid protein precursor/presenilin-1 transgenic mice, according to a prior study, without affecting the Alzheimer's like traits of acetylcholinesterase activity, oxidative stress or plaque deposition (Harrison et al., 2009). Dixit et al. (2015) reported that the results of their study conducted imply that as age increases, vitamin C deficiency may accelerate the start of oxidative stress in the brain, as well as play a key role in amyloid production, oligomerization and deposition. Javier et al. reported that during the early asymptomatic phases of Alzheimer's disease, the cerebrovascular response to hypoxia can be altered by vitamin C preventing beta secretase 1 production and amyloid β deposition while lowering the thickness of the cerebrovascular basement membrane (Frontiñán-Rubio et al., 2018).

Schizophrenia. Schizophrenia is a life-altering, chronic illness that causes functional impairment in the social, cognitive and emotional arenas. Positive symptoms (hallucinations and delusions) co-exist with negative symptoms (emotional blunting and apathy) and cognitive impairment (Brown and Roffman, 2014). Negative symptoms and cognitive deficiencies, on the other hand, do not usually react to antipsychotic therapy (Brown and Roffman, 2014). The case reported by Reuven Sandyk was about a patient suffering from schizophrenia since 17. The patient has been profoundly psychotic and has only partially responded to numerous psychotropic medicines. He has had practically total remission of psychotic symptoms since starting vitamin C therapy in 1987, and he is now able to work part-time. Even his relapse in early 1989 was much milder than previous relapses. Finally, his capacity to work part-time after being released from the hospital attests to the significant improvement in his mental state. This demonstrates the usefulness of vitamin C when used as a supplement in the treatment of a subset of persistent schizophrenia patients who do not have responded to the conventional treatments (Sandyk and Kanofsky, 1993). Dakhale et al. also reported that vitamin C supplementation when combined with atypical antipsychotics is responsible for the decrease in oxidative stress and improves schizophrenia outcomes. Forty-five patients took part in the study having schizophrenia. It was an 8-week, non-crossover, prospective, double-blinded trial. The primary finding of this study is that vitamin C supplementation with atypical antipsychotics resulted in a substantial drop in serum malondialdehyde and rise in plasma levels of AA in comparison to placebo with atypical antipsychotics (Dakhale et al., 2005).

Wound healing

AA is responsible for every aspect of wound healing including cellular apoptosis, synthesis of collagen, collagen synthesis and bone formation as well as antioxidant activities (Anderson, 2005). When wounding takes place, there is a drop in tissue and plasma levels. By using high-dose vitamin C supplements early in process of healing appears to be advantageous, especially if people who are already scorbutic (Long et al., 2003). Major difficulties caused by AA deficiency have traditionally been noted in scurvy patients; however, these defining traits are not always present in today's patients. AA deficit is more likely in patients having vascular disease, the elderly, pregnant women, smokers, drug abusers and persons who are underweight. According to the case study, oral vitamin C supplementation increased wound healing in those who had previously suffered from the deficit. The amount of AA in the blood was below than the standard value, that is, 25 μmol/L in 65 of 180 patients throughout a 21-month period (36%). Patients and their clinicians noticed a significant and rapid recovery of vast and intricate wounds after starting supplementation (1000 mg/day) (Bikker et al., 2016). Because exact AA levels can only be determined through laboratory testing, doctors must take a pragmatic approach and be on the watch for any

visible indicators of deficit in patients with a case of acute chronic wounds (Moores, 2013).

Iron deficiency anaemia

Iron deficiency anaemia is characterised by a decrease in red blood cells formation as a result of a total body iron deficiency (Brugnara, 2002). It is critical for the structure as well as the function of cells. Dietary iron is made up of both haeme and non-haeme iron. The divalent metal transporter-1 transports non-haeme ferrous iron into enterocytes (Frazer and Anderson, 2005). The basolateral membrane protein ferroportin is responsible for iron exiting enterocytes (Himmelfarb, 2007). Fe^{3+} is transported by transferrin from the bloodstream to haematopoietic organs and other tissues, including the liver (Graham et al., 2007). Macrophages in the reticuloendothelial system destroy aged red blood cells (Himmelfarb, 2007). Ferroportin is a protein that is responsible for release of iron from macrophages into the bloodstream. Iron is absorbed mostly in the region of duodenum and upper jejunum of intestine, where Fe^{2+} can be transferred into mucosal epithelial cells of small intestine. AA has shown to boost iron availability and availability from non-haeme iron sources (Hallberg, 1981). Vitamin C reduces synthesis of hepcidin and gives protection against anaemia caused by iron deficiency through altering the erythropoietin receptor in HepG2 cells as well as altering the bioavailability of iron (Chiu et al., 2012). Furthermore, ASC taken orally had a significant positive impact on haematological markers in the anaemic haemodialysis patients (Sirover et al., 2008). Darius et al. reported the ASC's effect on cellular iron absorption from Fe_2-Tf and they demonstrate that the physiological ASC concentrations considerably stimulate Tf-dependent iron uptake by variety of human cells (Lane et al., 2013). On contrary, randomised clinical trial reported that the findings call into question the recommendation that vitamin C supplements be taken in conjunction with iron orally in order to boost efficacy and accelerate anaemia recovery. In a moderately acidic environment, iron is absorbed as ferrous salt (Fe^{2+}). Vitamin C is thought to help in calcium absorption. However, based on the findings of this clinical investigation, vitamin C may not be as beneficial as previously assumed (Li et al., 2020).

Atherosclerosis

In the pathophysiology of vascular diseases, the endothelium plays a critical role (Iaccarino et al., 2004; Ross, 1986). Atherosclerosis is a degenerative condition of disease in which the major, as well as medium-sized arteries, are affected which is marked by loss of flexibility of the arterial wall and narrowing of the lumen (Rafieian-Kopaei et al., 2014). Localised thickening of the tunica intima causes the lumen to narrow. Myocardial infarction and ischaemic stroke are the most common symptoms of atherosclerosis. The antioxidant properties of vitamin C give an idea that it may help prevent cardiovascular disease (Moser and Chun, 2016). According to epidemiological data, antioxidant content in fruits and vegetables lowers the incidence of cardiovascular disease (CVD), which could be explained by the antioxidant's role in preventing oxidative alterations to low-density lipoprotein (LDL) (Salvayre et al., 2016). Scavenger receptors recognise oxidised LDL and integrate it into plaque (Li and Mehta, 2005). As a result, vitamin C's ability to prevent LDL oxidation may help to prevent atherosclerosis, potentially lowering CVD risk. Endothelial NO generation has been demonstrated to increase with AA, leading to increased vasodilation and lower blood pressure (d'Uscio et al., 2003). Furthermore, vitamin C may help make plaques more stable if atherosclerosis has been established by preventing vascular smooth muscle cell death (Siow et al., 1999).

Cancer

The debate over vitamin C's anti-cancer capabilities and its usefulness in palliative care has raged on very much (Zasowska-Nowak et al., 2021). Because of the development of resistance by cancer cells as well as toxicity, most chemotherapeutic drugs have restrictions on their usage (Ng et al., 2015). At high therapeutic levels, vitamin C has been demonstrated to have a particular influence on the cytotoxicity of many types of cancer cells (Pawlowska et al., 2019). There are number of processes through which vitamin C prevent and cure cancer. The processes are: boosting the immune system, increasing collagen production, blocking enzymes to prevent metastasis (spreading), prevention of cancer-causing viruses, the deficit of vitamin C in the patients suffering from cancer is treated, post-surgery wound healing in people with cancer improves chemotherapy efficiency, lowering chemotherapy toxicity, avoiding free radical damage and neutralising certain carcinogens (Chambial et al., 2013). Vitamin C's cytotoxic effects have been attributed to its capacity for the generation of reactive oxygen species (ROS) that has been linked to activating p53 which is tumour suppressor protein and the master regulator of DNA repair and death (Liu et al., 2015). Complementary and alternative medicine practitioners routinely administer vitamin C intravenously to treat infections, cancer and tiredness. Vitamin C's bioavailability and anti-cancer properties are known to be influenced by how it is administered in the body. Because high-dose IV has been already demonstrated in various multiple clinical studies to enhance the quality of life and health, it may be considered a palliative treatment (Zasowska-Nowak et al., 2021). SVCT1 does not appear to be important in cancer. According to various studies, SVCT2 plays a significant role in malignancies. The first discovered that when compared to normal cells, breast tumours exhibit greater levels of SVCT2 expression (Roa et al., 2020). Overexpression of this transporter enhanced chemosensitivity to the high dose of AA, resulting in to

Table 3. List of clinical trials for interventions of vitamin C (ascorbic acid) in other health conditions.

Serial number	Title	Study type	Population	Interventions	NCT number	Status	Key findings
1	Micronutrient to prevent noise-induced hearing loss	Interventional study	70 participants	Beta-carotene, vitamins C and E, magnesium	NCT00808470	Completed	Supplement had no effect on noise-induced changes in hearing
2	Quantitative in vivo biomarkers of oxidative stress in diabetes	Interventional study	42 participants	Vitamin C	NCT00845130	Completed	
3	Prophylaxis to reduce post-operative atrial fibrillation in cardiac surgery	Interventional study	304 participants	Beta blockers, amiodarone, ascorbic acid	NCT00953212	Completed	
4	ACTS trial	Interventional study	205 participants	Vitamin C, vitamin B1, hydrocortisone	NCT03389555	Completed	The combination did not show significant reduction in the SOFA score
5	Intravenous vitamin C in the treatment of viral infection especially in the treatment of shingles	Interventional study	68 participants	IV vitamin C	NCT00921934	Completed	The results showed that there was decline in the pain score which provide evidence that IV vitamin C is beneficial in treatment of viral infection
6	A study of vitamin C in the treatment of liver cancer to determine if it is safe and effective	Interventional study	5 participants	Ascorbic acid & sorafenib	NCT01754987	Completed	The safety data indicates no toxicity
7	A phase 2 pharmacokinetic study of 6r-bh4 alone or 6r-bh4 with vitamin C in subjects with endothelial dysfunction	Interventional study	52 participants	Sapropterin dihydrochloride and vitamin C	NCT00532844	Completed	
8	The effect of high-dose vitamin C on the liver function in chronic hepatitis patients	Interventional study	10 participants	High-dose vitamin C	NCT01413360	Completed	
9	Liposomal encapsulated vitamin C in complex regional pain syndrome	Interventional study	66 participants	Liposomal vitamin C versus vitamin C versus placebo	NCT04204200	Completed	There was no benefit to patients and no significant difference in time to heal the fracture
10	Ascorbic acid (vitamin C) infusion in human sepsis	Interventional study	24 participants	Ascorbic acid	NCT01434121	Completed	Ascorbic acid significantly reduced the proinflammatory biomarkers C-reactive protein and procalcitonin
11	Vit C-AF	Interventional study	20 participants	Vitamin C	NCT03148236	Completed	High dose of vitamin C is safe and well tolerated at the time of AF ablation and is associated with a blunted rise in C-reactive protein
12	CITRIS-ALI	Interventional study	170 participants	Infusion: vitamin C	NCT02106975	Completed	The infusion of ascorbic acid did not significantly improve the organ dysfunction scores
13	Study of high-dose vitamin C on outcome in cardiac surgery patients	Interventional study	57 participants	Drug: ascorbic acid Placebo: 5% Dextrose water or normal saline	NCT01167569	Completed	
14	VCSIP of infant lung infection	Interventional study	252 participants	Vitamin C	NCT01723696	Completed	
15	Does vitamin C reduce finger stiffness after distal radius fractures?	Interventional study	126 participants	500 mg vitamin C, 1 pill per day for 6 weeks versus 1 placebo pill for 6 weeks	NCT02216812	Completed	There was no difference in the finger stiffness
16	VICTAS	Interventional study	501 participants	Vitamin C, thiamine hydrocortisone	NCT03509350	Completed	
17	Vitamin C supplementation intervention	Interventional study	36 participants	Vitamin C 500 mg versus vitamin C 1000 mg versus placebo	NCT04036110	Completed	Patients with CHF acute intravenous administration of vitamin C enhances platelet responsiveness to the anti-aggregatory effects of NO donors and improves endothelial function

ACTS: Ascorbic acid, corticosteroids and thiamine in sepsis; AF: atrial fibrillation, CHF: congestive heart failure, CITRIS-ALI: vitamin C infusion for treatment is sepsis-induced acute lung injury; IV: intravenous; NCT: National Clinical Trial number; NO: nitric oxide; SOFA: Sequential Organ Failure Assessment; VCSIP: vitamin C to decrease effects of smoking in pregnancy; VICTAS: vitamin C, thiamine and steroids in sepsis; Vit C-AF: vitamin C in atrial fibrillation ablation.

increase in ROS production as well as cell death (Hong et al., 2013). Cancer cells, on the other hand, become resistant to the therapy when siRNA targeting SVCT2 is used. As a result, SVCT2 may have a role in ASC-mediated cancer cell killing (Hong et al., 2013). Table 3 represents the list of clinical trials for interventions of AA in other disease conditions.

Nutritional strategies for delivery of vitamin C

The hydrophilic character as well as the instability of vitamin C has led to its less utilisation. But, during recent years there are various types of studies conducted in order to improve the therapeutic outcome using vitamin C which includes nanoparticles and microparticles (Jang and Lee, 2008), liposomes (Hope et al., 1986), micelles (Sutradhar and Amin, 2014), microemulsion (Sawant et al., 2011) and orally disintegrating films (Garcia et al., 2018). This not only improved the therapeutic efficiency of vitamin C but also the drug targeting (Caritá et al., 2020).

Future perspective

AA is a vital and necessary component of human health. In humans, it is required for a number of physiological activities. Vitamin C is also been found to aid in the transportation of therapeutic agents in the body. Vitamin C has indeed been linked to a number of health advantages which includes antioxidant, anti-atherogenic, anti-carcinogenic and treatment of various neurodegenerative disorders. In recent decades, AA has been thoroughly studied and discovered to be an excellent antioxidant and cofactor in the synthesis of collagen. In preclinical and preliminary trials, vitamin C has been shown to increase organ function amid oxidative stress and inflammation. There are a certain number of ways in which AA reduces inflammation as well as oxidative damage has sparked a surge in interest in its medicinal use. The biggest limitation of the clinical trials of AA is that the study is not conducted on a large number of patients. Smaller groups of studies are conducted which cannot produce the results which can prove something concrete. The patients who are at high risk of COVID-19 suffering from vitamin C deficiency should be encouraged to start supplementation of vitamin C. There are several preclinical and clinical studies reported which highlights the role of vitamin C in COVID-19. There is more data required from the clinical trials which would prove the efficiency of vitamin C in COVID-19. The pending COVID-19 clinical trials may prove the potential benefits of vitamin C in COVID-19.

Conclusion

There is high prevalence of deficiency of vitamin C worldwide. Vitamin C may not be the first-line treatment, but may be considered as a safe, adjuvant as well as inexpensive nutritional supplement therapy for many diseases as mentioned in this review article. The public health sector should take an account of vitamin C deficiency and should do necessary things for the public in order to reduce the patients suffering from deficiency of vitamin C.

Abbreviations

5-HT	5-hydroxytryptamine
AA	ascorbic acid
APP/PSEN 1	amyloid protein precursor/presenilin-1;
ARDS	acute respiratory distress syndrome
ASC	ascorbate
cGMP	cyclic guanosine monophosphate
CVD	cardiovascular disease
DHA	dehydroascorbate
DOPA	dihydroxyphenylalanine
dUCH	*Drosophila* ubiquitin C-terminal hydrolase
ET-1	endothelin-1
GABA	gamma amino butyric acid
GLUT	glucose transporter
ICAM-1	intercellular adhesion molecule 1
ICU	intensive care unit
IL-1	interleukin-1
IL-6	interleukin-6
IL-8	interleukin-8
IV	intravenous
LDL	low-density lipoprotein
NF-κB pathway	nuclear factor kappa B pathway
NMDA	N-methyl-D-aspartic acid or N-methyl-D-aspartate
NO	nitric oxide
RDA	recommended dietary allowance
ROS	reactive oxygen species
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLC23A	solute carrier family 23 m1
SNP	single nucleotide polymorphism
SVCT	sodium ascorbate co-transporter
TNF-α	tumour necrosis factor alpha

Acknowledgements

All the figures are partially created with 'Biorender.com'.

Authors' contribution

All the authors contributed equally to prepare this article, read and approved the final manuscript.

Consent for publication

All the authors have agreed to submit this paper for publication in Nutrition and Health.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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