Review Article

Vitamin C and human diseases: An overview

Suhera M. Aburawi

Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya

Mediterranean Journal of Pharmacy and Pharmaceutical Sciences

Article information

Received
24-10-2021
Revised
07-11-2021
Accepted
11-12-2021
Published
31-12-2021

Corresponding Author
smaburawi@gmail.com

Abstract

Vitamin C is associated with history of the cause of the ancient hemorrhagic disease scurvy. Vitamin C is an essential nutrient with important antioxidant properties. It is required by the body for normal physiological function. The body cannot synthesize vitamin C, it is present in nature through foods and other natural sources and it exists as a nutritional food supplement. The antioxidant activity of vitamin C protects the body from free radical damage. Vitamin C is essential for the development and maintenance of connective tissues. It is used as therapeutic agent in many diseases and disorders. Vitamin C plays an important role in several metabolic functions, as the conversion of the amino acid, tryptophan, to the neurotransmitter, serotonin, and the conversion of cholesterol to bile acids. Vitamin C supplementation resulted in a significant increase in vitamin C levels in populations; its high intake is associated with positive effects on cardiovascular risk factors. Vitamin C protects the immune system, reduces the severity of allergic reactions and helps to fight infections. It has an important role in bone formation, wound healing and the maintenance of healthy gums. There is profound beneficial effect of vitamin C in respect to human diseases as cancer, atherosclerosis, diabetes, neurodegenerative disease and many metal toxicities. Several vitamin C analogs have been produced as anticancer and antioxidant activity. Vitamin C is useful if it is used as adjuvant therapy for several chronic diseases. Thus, this review summarizes the importance of vitamin C in the body's physiology and biochemistry, in addition, the different mechanisms that vitamin C is implicated to treat different acute and chronic diseases. Future exploration should pay attention to chronic disease management by vitamin C.

DOI 10.5281/zenodo.5805947

Keywords: Ascorbic acid, chronic disease, disease, metabolic disorders, prevention, vitamin C

HOW TO CITE THIS: Aburawi SM (2021) Vitamin C and human diseases: An overview. Mediterr J Pharm Pharm Sci 1(4): 25-36. https://doi.org/10.5281/zenodo.5805947

Introduction

Vitamin C (ascorbic acid) is a vital nutrient for health and is an essential vitamin required by human bodies for normal physiological function [1, 2]. It is an antioxidant that protects the body from free radical damage [3] and deleterious effects of pollutants and toxins. Vitamin C is an essential nutrient involved in many biological and biochemical processes as an antioxidant; it prevents the development of various diseases due to oxidative damage [4]. Human bodies are unable to synthesize vitamin C due to the absence of gluconolactone oxidase enzyme, which is required for the formation of vitamin C from glucose and galactose [3]. Therefore, they must obtain it from dietary sources [5]. Vitamin C has widely been found in citrus fruits, strawberries, tomatoes, broccoli, Brussels sprouts, green peppers, red peppers, turnips, and many other leafy vegetables [6]. It plays a central role in the antioxidant defense system and exists in two major forms. The charged form, ascorbate, is taken up into cells via sodium-dependent facilitated transport. The uncharged form, dehydroascorbate, enters cells via glucose transporter, then converted back to ascorbate within these cells [7]. Its absorption in the buccal cavity is by passive diffusion and in the gastrointestinal tract absorption is by active sodium-dependent vitamin C transporters (SVCT)

[8, 9]. Bioavailability of vitamin C is reduced in stress, alcohol intake, smoking, fever, viral illnesses, antibiotics, and pain killers use; also observed when exposure to petroleum products or carbon monoxide and heavy metals toxicity. Low vitamin C levels in the body could be due to increased utilization and/or decreased absorption from the gut [3]. Vitamin C metabolites are primarily eliminated through urine [6]. The concentration in the body represents a very sensitive index of oxidative stress [10].

Antioxidant micronutrients and antioxidant enzymes are considered the body's defense systems against free radicals and reactive molecules. The production of highly reactive oxygen metabolites is normal in cellular metabolism. The formation of the highly reactive oxygen metabolites is needed in the body's natural immune system, mitochondrial respiratory chain, arachidonic acid metabolism, ovulation and fertilization [11]. The excessive production of free-radical species is continuous in the human body which indicates pathological condition [11]. The body requires vitamin C, for normal physiological functions. It helps in the synthesis and metabolism of tyrosine, folic acid and tryptophan, hydroxylation of glycine, proline, lysine carnitine and catecholamine [3]. Vitamin C is present with a high concentration in the adrenal gland, where it is required both in catecholamine biosynthesis and in adrenal steroidogenesis [12]. It facilitates the conversion of cholesterol into bile acids and hence lowers blood cholesterol levels [3]. It increases the absorption of iron in GIT by reducing ferric to ferrous state [3]. It was observed that vitamin C in vitro acts as an antioxidant by preventing iron-induced lipid peroxidation [13]. It was reported that orally supplemented vitamin C in guinea pigs with iron overload acts as an antioxidant by suppressing lipid oxidation [14]. In healthy humans, vitamin C at 40 - 80 µM of plasma concentration exerts antioxidant activity, in which vitamin C donates an electron to free radicals and reduces the potentially damaging effects [15]. At the same time, vitamin C is oxidized into unreactive ascorbate radical, which is converted back to vitamin C through NADH/NADPH-dependent reductases [15]. As an antioxidant, vitamin C repairs the tocopheroxyl radical of vitamin E, permitting vitamin E to function again as an antioxidant [16]. Vitamin C protects DNA, amino acid residues and lipids from oxidation induced by free radicals and maintains their integrity [17], preventing them from harmful mutations [2]. Decreased blood levels of vitamin C are associated with diabetes mellitus [18], acute pancreatitis [19], asthma [20] or an unstable coronary syndrome [21]. Deficiency of vitamin C is observed with anemia, infections, bleeding gums, scurvy, poor wound healing, capillary hemorrhage, muscle degeneration, atherosclerotic plaques and neurotic disturbances. Large doses of vitamin C are required to correct the deficiency, and unlike fat-soluble vitamins, toxicity is rare [3]. Vitamin C intake for reduction of chronic disease risks such as cancer and cardiovascular diseases should be higher than the recommended dietary allowances (RDA) [22].

Vitamin C and survey

Low levels of vitamin C in the body can lead to scurvy [1]. People needed just 10 mg of vitamin C per day to avoid scurvy [23].

Vitamin C and common cold

Vitamin C has a known health beneficial effect in prevention and relief of common cold [24]. In the common cold, the immunity is attenuated. Vitamin C boosts immunity during rhinitis; it stimulates the immune system by enhancing T-cell proliferation in response to infection. These cells are capable of lysing infected targets by producing large quantities of cytokines and by helping B cells to synthesize immunoglobulins to control inflammatory reactions. Also, vitamin C blocks pathways that lead to apoptosis of T-cells and stimulate or maintain T-cell proliferation to attack the infection [3]. The antioxidant properties of vitamin C are useful during the common cold. In an infection, phagocytic leukocytes activation produces oxidizing compounds that are released from the cells. Vitamin C reacts with these oxidants and may decrease the inflammatory effects that they produce [25]. Several clinical trials of vitamin C, with different doses, showed that it does not have a significant prophylactic effect, but reduces the severity and duration of symptoms of cold during the period of infection [26].

Vitamin C and cardiovascular diseases

Diet rich in fruits and vegetables is highly protective against atherosclerosis and coronary heart disease [27]. Frequent intake of fruit and vegetables, that are rich in vitamin C, increases the activity of the fibrinolytic system by lowering plasminogen activator inhibitor activity [28]. Increased fibrinogen concentrations increase the risk of acute or chronic infection and cardiovascular disease. Administration of vitamin C in a dose of 2 gm per day, increases fibrinolytic activity and decreases the platelet adhesive index and serum cholesterol [29]. Vitamin C is important for the production of collagen, which plays a role in heart health by maintaining blood vessel walls [23]. Daily administration of vitamin C is useful to control blood pressure in hypertensive patients [30]. The higher serum levels of vitamin C significantly lower systolic and

diastolic blood pressure among middle-aged or elderly populations [31, 32]. The powerful antioxidant effect of vitamin C reverses endothelial dysfunction due to increased oxidative stress, and prevents hyperoxic vasoconstriction [33]; it also improves lipid-induced impairment of endothelium-dependent vasodilation [34]. Vitamin C may improve nitric oxide production, [1] that relaxes and widens blood vessels [35]. Total cholesterol, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) are considered major risk factors for cardiovascular disease [36]. Oxidation of lipoproteins may promote atherosclerosis [37]. The oxidized LDL has an atherogenic potential due to lipid peroxidation [38]. Vitamin C protects against neutrophil-mediated LDL oxidation; this may be due to the scavenging of extracellular oxidants, also prevents pro-oxidant effects of urate in LDL oxidation [39]. Vitamin C may protect from atherosclerosis by strengthening the artery walls through its participation in the synthesis of collagen and preventing the undesirable adhesion of white blood cells to damaged arteries [40]. A clinical study concludes that co-administration of vitamin C with the regular use of anti-hypertensive drugs helped in decreasing systolic and diastolic blood pressure of hypertensive patients compared to patients with antihypertensive therapy only. Further, the use dose of vitamin C (500 mg/day) induced a significant increase in vitamin C plasma concentrations accompanied by a reduction in LDL, TC, TG and an increase in the beneficial HDL [41].

Vitamin C and neuropsychiatric disorders

Oxidative stress may play a role in neurodegenerative diseases, such as Alzheimer's disease that causes dementia and is associated with aging [42]; also Schizophrenia, is associated with morbidity and economic burden [3]. Several studies investigated the role of increased free radical generation in the pathogenesis of schizophrenia. In schizophrenics, it was detected that there are changes in the optimum activities of antioxidant enzymes [43, 44] and related parameters of lipid peroxidation [45, 46] in blood. The brain contains a large amount of unsaturated fatty acids, and catecholamine, which are considered the target molecules for lipid peroxidation [47, 48]. A significant rise in oxidative stress and decreased antioxidant status was observed in the chronic stage of schizophrenia as compared to those in acute condition [3]. A decrease in the levels of vitamin C was found in schizophrenics compared to normal controls. Vitamin C supplement produces a reduction in a brief psychiatric rating scale (BPRS) and positive and negative syndrome scale score [49]. Vitamin C, an antioxidant vitamin, plays an important role in protecting free radical-induced damage in the brain [3]. The increase in dehydrovitamin C and fall in reduced vitamin C at the same time suggests scavenging action of vitamin C and its utilization with increased oxidative stress as indicated by high blood malondialdehyde levels [50]. A clinical study found that co-administration of vitamin C with antidepressants therapy decreased significantly the total Hamilton Depression Rating Scale (HDRS) scores. Vitamin C was therapeutically benefited with an antidepressant in the treatment of depression and predicts a good response; it was well tolerated and effective in improving depressive symptoms [51].

Vitamin C and cancer

In the human body, reactive oxygen species (ROS) are generated during physiological and pathological processes [52] but high levels of ROS contribute to carcinogenesis [53]. ROS attacks cellular DNA causing damage and genomic instability leading to mutations that incorporate the development of neoplastic characteristics [54]. Antioxidant activity of vitamin C may help reduce inflammation and decrease the risk of developing various conditions of cancers [1]. It was shown that vitamin C may have a role in cancer prevention [4]. In a clinical study of elderly patients with acute myeloid leukemia, vitamin C with anticancer agents had a better rate of complete remission and overall survival without any substantial toxicity as compared to the anticancer agents alone [55].

A high dose of vitamin C is important for exerting the anticancer effect [2]. Evidence that vitamin C alone may not be effective enough in the treatment of most active cancers, but it improves the quality of life and extends longevity in cancer patients. Therefore, vitamin C should be given as a supplement in cancer therapy [6]. High-dose of vitamin C administration improved the survival of patients with terminal cancer [56, 57]. In vitro study showed that a high concentration of vitamin C is toxic to cancer cells [58]. Intravenous administration of vitamin C may act as a pro-drug for the formation of hydrogen peroxide, causing the death of cancer cells without affecting the normal cells [59]. Vitamin C produces apoptosis of cancer cells by acting as pro-oxidant and increasing intracellular reactive oxygen species levels [60]. Mechanisms involved of vitamin C in the treatment and prevention of cancer are: enhancing the immune system; stimulating the formation of collagen; preventing

metastasis by inhibiting enzymes; preventing viruses that can cause cancer; correction of vitamin C deficiency, which is often associated with cancer patients [61]. Experimental and clinical studies observed that high vitamin C concentration leads to tumor shrinkage [59, 62]. Intravenous vitamin C administration in cancer therapy selectively kills tumor cells in vitro. This tumor-killing phenomenon is because of the pro-oxidant property of vitamin C, due to the production of hydrogen peroxide [59]. Vitamin C generates H_2O_2 in cancer cells [63] through metals reduction such as copper and iron reaction [64], leading to selective cytotoxicity to cancer cells [63]. Vitamin C, as an antioxidant, enhances the effectiveness of chemotherapy and reduces its toxicity, and increases survival rate [61, 65]. Administration of vitamin C decreases the formation of nitrosamines, which is associated with gastric cancer [66]. Lipophilic derivative of vitamin C as Ascorbyl stearate can cross the cell membranes and blood-brain barrier; it inhibits cell proliferation by interfering with cell cycle and induces apoptosis by modulation of insulin-like growth factor 1-receptor expression in T98G and pancreatic cancer cells [67]. Vitamin C hinders cancer progression by targeting different susceptive nodes such as Hypoxia-inducible factor (HIF), Glucose transporter 1 (GLUT1), and mutated genes of ten-eleven translocation (TET) enzymes. It is known that Hypoxia-inducible factor 1 (HIF-1) activates the transcription of genes that are involved in crucial aspects of cancer biology, including cell survival, glucose metabolism, and invasion [68]. Hypoxia-inducible factor controls the expression of genes linked to angiogenesis, anti-apoptotic activity, stem cell renewal, metastasis, and therapeutic resistance of cancer cells [2]. Higher doses of vitamin C reduce DNA damage and mutations through degradation of HIF-1α levels [69]. Cancer cells must increase glucose uptake, to ensure the flux of sugar into metabolic pathways; therefore, GLUT1 is an important target in cancer treatment [22]. Targeting GLUT1 activity is a promising strategy for the development of drugs aimed at treating neoplastic growth [70]. Mutated genes (TET) proteins are associated with the activation of cancer stem cells by altering the metabolic and epigenetic profiles of cells [2]. The activity of TETs is an important factor in numerous developmental stages in physiological function, and disruption can lead to failure of cell type-specific functions [71]. Disruption of the ten-eleven translocation (TET) is an early event in the onset of disease. It is now known that all three TET genes are mutated and show reduced expression, and the proteins have impaired activity in a wide range of different cancer types [71]. DNA methylation abnormalities are often observed in diseases. The ten-eleven translocation (TET) enzymes oxidize 5-methylcytosines (5 mCs) and promote locus-specific reversal of DNA methylation [71].

Vitamin C and diabetes mellitus

Diabetes mellitus is associated with increased production of reactive oxygen species and a reduction in antioxidant defenses [7, 72]. Oxidative stress is a common pathogenetic factor of diabetic nephropathy [7]. Tubular epithelial cells are dehydroascorbate dependent; a decrease in vitamin C levels in tubular epithelial cells through competition of glucose and dehydroascorbate for common transport mechanism in diabetes will deprive the cells of antioxidant, this may lead to reactive oxygen species accumulation [7]. Insulin increases the active cellular uptake of vitamin C, while hyperglycemia inhibits renal vitamin C reabsorption. Because dehydroascorbate and glucose compete for glucose transporters, hyperglycemia discharges vitamin C from tubular epithelial cells, resulting in decreased antioxidant capacity [7].

Vitamin C and fertility

Vitamin C is essential for the structural and functional integrity of androgen-dependent reproductive organs [3]; its concentration in seminal plasma is higher than plasma concentration [73], and the percentage of sperm with normal morphology correlated significantly with seminal vitamin C levels [3]. The deficiency of vitamin C may produce oxidative damage induced by reactive oxygen species (ROS); an increase in ROS was observed in the semen of infertile men [74]. In a human trial, a decrease in vitamin C levels was associated with an increase in seminal plasma lipid peroxidation [75]; it may also lead to abnormal sperm parameters [76]. Low concentration of vitamin C produced marked degenerative changes in the testes, epididymis, and vas deferens of scorbutic guinea pigs [77], also produced degeneration of the spermatogenic epithelium, steroidogenesis, and decline in plasma testosterone levels [78]. As an antioxidant, vitamin C improves sperm quality in a dose-dependent manner in men [79], increases progesterone levels in infertile women with luteal phase defect [80]. An animal experimental study showed that vitamin C improves antioxidant enzymes activity and reduces malondialdehyde (MDA) in testis [81]. It was reported that vitamin C supplementation leads to a significant reduction in ROS concentration [82], sperm membrane

lipid peroxidation [83] and sperm DNA oxidation [82], and increased sperm quality [83]. Polycystic ovary syndrome induced by formaldehyde produces a histological alteration in the ovary and uterus of female mice reproductive system; vitamin C administration has prophylaxis and treatment role against this damage induced by formaldehyde [84].

Vitamin C and atherosclerosis

Development of atherosclerosis may be due to lipid peroxidation and oxidative modification of LDL [85]; initiation of atherosclerosis can be due to adhesion of leukocytes to the endothelium. Vitamin C helps in the prevention of atherosclerosis by strengthening the artery walls through its participation in the synthesis of collagen, and by preventing the undesirable adhesion of white blood cells to damaged arteries [85]. In vivo studies showed that vitamin C inhibits leukocyte-endothelial cell interactions induced by cigarette smoke [86]. Vitamin C, as an antioxidant, scavenges free radicals and thus prevents the oxidation of LDL [39], even in passive smokers [87]. A deficiency of vitamin C leads to enhance the accumulation of cholesterol in the thoracic aorta along with pathomorphological changes in blood vessels [3], also leading to impaired cholesterol metabolism resulting in atheromatous changes in the vascular system [88]. High intake of vitamin C reduces the risk of stroke in half compared to those with the lowest intake [89]. A cohort study suggested that cardiovascular mortality was reduced in both sexes by vitamin C [90]. Vitamin C administration causes a significant reduction in LDL and a nonsignificant increase in HDL and protects against coronary artery disease [91].

Vitamin C and asthma & obstructive pulmonary disease

Vitamin C plays an essential role in defending against oxidant attack in the airways; its deficiency in asthmatics sputum may be a factor in the pathophysiology of asthma or a response to asthmatic airway inflammation [25].

Vitamin C and immunity

In humans, vitamins C has immune potentiating benefit [4], while in guinea pigs, increases serum levels of antibodies [92]. Vitamin C concentrations in the plasma and leukocytes rapidly decline during infections and stress [93]. Administration of vitamin C improves the human immune system such as antimicrobial and NK cell activities, lymphocyte proliferation. Vitamin C maintains the redox integrity of cells and protects them against ROS generated during the respiratory burst and in the inflammatory response [93]. Vitamin C reverses the damage caused by free radicals at a cellular level, modulates immune cell functions through the regulation of redox-sensitive transcription factors, and affects the production of cytokines and prostaglandins [3]. Intravenous vitamin C treatment reduces pro-inflammatory cytokines IL-1α, IL-2, IL-8, TNF-α [94]. Vitamin C inhibits the excessive activation of the immune system leading to prevent tissue damage; it supports antibacterial activity [95]. A study conclude that vitamin C showed a significant antibacterial effect on both Gram-positive and Gram-negative bacteria and enhanced the effect of the Penicillin G [96].

Vitamin C and allergies

There is evidence that low vitamin C levels were common in people with allergies [1]. During an allergic reaction, the immune system triggers an inflammatory response that leads to symptoms such as swelling and hives. During this process, the body produces ROS, which leads to oxidative stress [1]. A high dose of vitamin C (IV) may help reduce allergy symptoms [1].

Vitamin C and tissue healing

Wound healing requires synthesis and accumulation of collagen and subsequent cross-linking of the fiber for new tensile strength to the damaged tissue [97, 98]. Vitamin C is important for the production of collagen, which binds together wounds, allowing them to heal [23]. Vitamin C is necessary for the normal healing process especially for post-operative patients; its administration is recommended to accelerate the healing process [99]. In clinical studies, evidence that wound healing in subjects not deficient in vitamin C significantly accelerated with vitamin C daily dose [99]. In cultured human keratinocytes, vitamin C acts as a modulator of proliferation and differentiation, directly affecting the keratinocyte or indirectly through effects on fibroblasts [100]. Vitamin C modulates the growth and maturation of chondrocytes and accelerates bone fracture healing [101].

Vitamin C and pain

Vitamin C has analgesic effect for neuropathic pain [102]. Antinociceptive action of vitamin C is through the activation of the dopamine pathway, as this effect was blocked by metoclopramide. Vitamin C may also modulate its analgesic effect through 5HT release [102]

because this action was inhibited by ondansetron [103]. In addition, vitamin C may produce its antinociception by interaction with ionotropic glutamate receptors; NMDA receptor is involved during neuropathic pain which is redox-regulated [104] for these reasons, arachidonic acid could possess a role in modulating nociceptive processes. In addition, vitamin C inhibits p38-dependent nociceptive signaling in spinal cord microglia and dorsal root ganglia neurons [105].

Vitamin C and pain pollution

Air pollution consists of various substances and chemicals that may produce a negative impact on people's health. Vitamin C with antioxidant effect may reduce symptoms of asthma and chronic obstructive pulmonary disease [1].

Vitamin C and cataract

Vitamin C is found in high concentrations in the lens, and is important for the prevention of cataracts in the older population [106]. It is believed that oxidative stress may be a factor in the conditions; therefore, vitamin C could be useful with its antioxidant activity [1].

Vitamin C and anemia

Vitamin C is known to enhance the availability and absorption of iron from non-heme iron sources [107]. It enhances the absorption of iron; healthcare professionals recommend taking vitamin C supplements with iron tablets to improve absorption in people with iron deficiency anemia [1]. Observations showed that vitamin C inhibits the expression of hepcidin [108]; hepcidin is the master regulator of systemic iron homeostasis, tightly influences erythrocyte production. High hepcidin levels block intestinal iron absorption and macrophage iron recycling, causing iron-restricted erythropoiesis and anemia [109]. Vitamin C is a novel modulator for the classical transferrin Fe+ uptake pathway, acting through intracellular reductive mechanism [110].

Vitamin C and cigarette

Cigarette smokers are exposed to a large number of oxidants [111]. Vitamin C levels in the plasma of smokers were depleted by smoking compared to nonsmokers [112].

Cigarette smoking is associated with endothelial dysfunction with impaired endothelium-dependent flow-mediated dilation [113]. Vitamin C improves the endothelial function in chronic smokers and restores impaired coronary flow velocity reserve against oxidative stress in smokers [114].

Vitamin C and DNA

In the human body, reactive oxygen species (ROS) attacks cellular DNA and produce damage and genomic instability; this leads to mutations and the development of neoplastic disorders [54]. High vitamin C intake protects DNA, amino acid residues, and lipids from oxidation induced by free radicals and maintains their integrity [17], preventing them from harmful mutations [2]. The deficiency of vitamin C produces damage to DNA by causing single- and double-strand breaks and oxidative lesions [115].

Vitamin C pre-oxidant role

Vitamin C in micromolar concentrations has anti-oxidant activity, while in millimolar concentrations has pro-oxidant activity. The pro-oxidant activity is useful in inducing cytotoxicity to tumor cells [116]. In an experimental study, vitamin C in millimolar concentrations donates an electron to copper and iron metals, leading to the production of superoxide, hydrogen peroxide-like ROS [64]. Vitamin C reduces Fe^{3+}/Cu^{2+} to ferrous (Fe^{2+})/cuprous (Cu+) ions and oxidizes itself into ascorbate free radical (Asc−). The reduced Fe^{2+}/Cu+ ions react with oxygen to form ROS such as superoxide radicals, leading to the formation of hydrogen peroxide (H_2O_2). Hydrogen peroxide is catalyzed by Fe^{2+}/Cu+, yielding hydroxyl peroxide radical (HO·) [16, 117].

Vitamin C and toxicity

High consumption of vitamin C and its metabolites such as dehydrovitamin C, 2,3-diketogulonic acid, and oxalic acid is excreted via the kidney in humans; it may cause gastrointestinal disturbances or diarrhea [118]. Vitamin C in the presence of heavy metal results in the production of ROS as superoxide ion, hydrogen peroxide, and hydroxyl radical; this enhances lipid peroxidation, DNA damage, and altered calcium and sulfhydryl homeostasis [3]. Vitamin C metabolism will break down in tissues to dehydrovitamin C, then to diketogulonic acid, and then catabolized to oxalate, which is excreted in urine [119]. Documented cases that daily intake greater than 2 gm per day can induce oxalate crystal nephropathy [120]. The supersaturated oxalate in the tubules leads to deposits as crystals and develops stones that in turn damage the tubular epithelium [121]. Oxalate nephropathy induced by vitamin C can lead to chronic renal disease; this may need long-term dialysis or transplantation, and even death [122]. Cadmium is an extremely toxic metal commonly found in industrial workplaces, it causes lipid

peroxidative changes in various tissues. Vitamin C intake has a protective role in the lung and brain of rats exposed to excessive cadmium [123]. Vitamin C restores the hematological changes in mercury and cadmium exposed Wistar rats [124]. Vitamin C also has a protective function against concomitant exposure to heavy metals and radiation [125]. Experimental studies report the beneficial effect of vitamin C against heavy metal toxicity. Lead is the common environmental poison in which vitamin C has a protective role [126]. A study showed that lead-induced electrophysiological changes in rat colon; were inhibited by vitamin C administration [127]. Arsenic toxicity is essentially associated with lipid peroxidation and oxidative stress. Arsenic in drinking water may even cause chromosomal aberration leading to molecular disorders [128]. Arsenic exposure during gestation and lactation leads to increased lipid peroxidation in the rat brain, which was reversed by vitamin C administration [129]. Arsenic induced hepatotoxicity; vitamin C supplementation improves mitochondrial structure and function along with restriction of apoptosis due to caspase-3 inhibition in arsenic trioxide exposed rat liver [130].

Interaction and Vitamin C

Clinical study showed that the administration of vitamin C combined with antidepressant therapy reduced Hamilton depression rating scale compared to the antidepressant therapy effect without vitamin C administration. This indicates that vitamin C improves antidepressant therapy and reduces their side effects [51]. The same clinical study showed that agitation, anxiety (psychotic and somatic) and hypochondrias were improved by vitamin C administration. Symptoms of depression that improved with vitamin C administration are depressed mood, feeling of guilt, suicide, early insomnia, middle insomnia, late insomnia, weight loss [131]. Using Cup Cut Diffusion Method, Vitamin C showed a significant antibacterial effect on both Gram-positive and Gram-negative bacteria and enhanced the effect of penicillin G [96]. In a study using the same technique, vitamin C produced an inhibitory effect on the growth of gram-positive and gram-negative bacteria. Vitamin C potentiated the effect of ciprofloxacin at low concentrations (10 mg/ml), while vitamin C at higher concentrations (20 and 40 mg/ml) antagonized the inhibitory effect of ciprofloxacin on gram-positive and gram-negative bacteria [132]. Using averted gut sac technique of albino rats, Vitamin C absorption was increased by time, either alone or in the presence of black tea extract. Black tea extract increased the absorption of vitamin C compared to the absorption of vitamin C alone [133]. A neurobehavioral study showed that vitamin C produced dose-dependent anxiolytic effects, using albino rats. The combined treatment of vitamin C with Alprazolam did not potentiate the anxiolytic action, but it has additive effects [35, 134, 135]. Acute administration of vitamin C was accompanied by an increase in GABA levels in almost all brain areas studied, leading to anxiolytic action [134]. Flumazenil and Picrotoxin abolished the anxiolytic action of vitamin C in elevated plus-maze; this indicates that the action of vitamin C is mediated through the benzodiazepine/$GABA_A$ receptor. Vitamin C levels in the brain were found to be regionally dependent: higher levels were found in the anterior regions, such as the cerebral cortex and mid-brain, with progressively lower levels in more-posterior regions, such as the brainstem and cerebellum. Alprazolam did not affect vitamin C levels in all brain areas studied [135]. Vitamin C causes a significant change in the pharmacological effects of some drugs, which may lead to unpredictable responses. Recently, vitamin C decreases extrapyramidal side effects caused by the antipsychotic haloperidol; it successfully decreases catalepsy, ptosis, rigidity and akinesia in mice [136].

The body needs vitamin C for various functions. Vitamin C helps the body produce collagen and some neurotransmitters. It acts as an antioxidant; it helps remove reactive oxidative species (ROS) from the body; it helps the body absorb iron. It boosts the immune system. It enhances wound healing [1]. Vitamin C is safe in healthy individuals; the recommended daily dietary dose of vitamin C is approximately 100 mg [121]. High doses of vitamin C for the treatment of various conditions from the common cold to cancer. Vitamin C has been widely used in the treatment and prevention of a large number of chronic disorders like diabetes, common cold, cataracts, glaucoma, macular degeneration, stroke, heart diseases, and cancer [3]. Vitamin C induced a reduction in blood lipid levels in normal and hypercholesterolemic subjects [3], which may protect from atherosclerosis. Vitamin C produces a dose-dependent effect, as antioxidant or anticancer activity; at lower concentrations, it functions as an antioxidant, and at higher pharmacological concentrations, as a pro-oxidant [137]. Vitamin C may be useful for cardiovascular health; as an antioxidant, it helps widen the blood vessels, improve nitric oxide production, and help reduce plaque instability in atherosclerosis; it can protect against heart disease and hypertension [1]. There is a negative correlation between serum vitamin C and total cholesterol [138], and positive correlations between serum vitamin C

and HDL [139]; vitamin C may involve in cholesterol metabolism [4]. Supplement therapy of vitamin C is used as adjuvant therapy; it is useful in patients with stress-induced psychiatric disorders [140]. Vitamin C has a beneficial effect in neurodegenerative diseases as Alzheimer's disease [141]. Vitamin C may help lower the risk of cataracts and slow the progression of age-related macular degeneration, this benefit may be due to vitamin C's antioxidant activity [1]. Vitamin C protects against metal-induced hepatotoxicity [130]. Evidence suggests that vitamin C is a powerful antioxidant in biological systems. In vivo markers of oxidative damage are developed; future studies of the antioxidant effects of vitamin C should target patient groups at high risk of oxidant damage. Moderate intake of vitamin C may produce a hypocholesterolemia effect, and long-term supplementation of vitamin C may be used to keep the lipid profile within normal limits. Vitamin C may have a benefit if it is taken as co-adjuvant therapy by patients with chronic disease.

Ethical issues

Including plagiarism, Informed Consent, data fabrication or falsification and double publication or submission have completely been observed by the author.

Conflict of interest

The author declared no competing interest.

References

1. Nordqvist J (2021) Vitamin C: Why is it important? Medically reviewed by Alan Carter. January 4, 2021. https://www.medicalnewstoday.com/articles/219352.
2. Reang J, Sharma PC, Thakur VK, Majeed J (2021) Understanding the therapeutic potential of ascorbic acid in the battle to overcome cancer. Biomolecules. 11 (8): 1130. doi.org/10.3390/biom11081130.
3. Chambial S, Dwivedi S, Shukla KK, John PJ, Sharma P (2013) Vitamin C in disease prevention and cure: an overview. Indian Journal of Clinical Biochemistry. 28 (4): 314-328. doi:10.1007/s12291-013-0375-3.
4. Domitrović R (2006) Vitamin C in disease prevention and therapy. Biochemia Medica (Zagreb). 16: 107-125. doi: 10.11613/BM.2006.011.
5. Smirnoff N (2001) L-ascorbic acid biosynthesis. Vitamins and Hormones. 61: 241-66. doi: 10.1016/s0083-6729(01)61008-2.
6. Naidu KA (2003) Vitamin C in human health and disease is still a mystery? An overview. Nutrition Journal. 2 (1): 7. doi: 10.1186/1475-2891-2-7.
7. Chen L, Jia RH, Qiu CJ, Ding G (2005) Hyperglycemia inhibits the uptake of dehydroascorbate in tubular epithelial cell. American Journal of Nephrology. 25 (5): 459-65. doi: 10.1159/000087853.
8. Szarka A, Lőrincz TA (2013) C-vitamin celluláris, intracelluláris transzportja. Fiziológiai vonatkozások [Cellular and intracellular transport of vitamin C. The physiologic aspects]. Orv Hetil. 154 (42): 1651-1656. Hungarian. doi: 10.1556/OH.2013.29712.
9. Wilson JX (2005) Regulation of vitamin C transport. Annual Review of Nutrition. 25: 105-125. doi.org/10.1146/annurev.nutr.25.050304.092647.
10. Kojo S (2004) Vitamin C: basic metabolism and its function as an index of oxidative stress. Current Medicinal Chemistry. 11 (8): 1041-1064. doi: 10.2174/0929867043455567.
11. Ahmad IM, Aykin-Burns N, Sim JE, Walsh SA, Higashikubo R, Buettner GR, Venkataraman S, Mackey MA, Flanagan SW, Oberley LW, Spitz DR (2005) Mitochondrial O2*- and H2O2 mediate glucose deprivation-induced stress in human cancer cells. Journal of Biological Chemistry. 280 (6): 4254-4263. doi: 10.1074/jbc.M411662200.
12. Patak P, Willenberg HS, Bornstein SR (2004) Vitamin C is an important cofactor for both adrenal cortex and adrenal medulla. Endocrine Research. 30 (4): 871-875. doi: 10.1081/erc-200044126.
13. Suh J, Zhu BZ, Frei B (2003) Ascorbate does not act as a pro-oxidant towards lipids and proteins in human plasma exposed to redox-active transition metal ions and hydrogen peroxide. Free Radical Biology and Medicine. 34: 1306-1314. doi: 10.1016/s0891-5849(03)00147-3.
14. Chen K, Suh J, Carr AC, Morrow JD, Zeind J, Frei B (2000) Vitamin C suppresses oxidative lipid damage in vivo, even in the presence of iron overload. American Journal of Physiology. Endocrinology and Metabolism. 279: 1406-1412. doi: 10.1152/ajpendo.2000.279.6.E1406.
15. Du J, Cullen JJ, Buettner GR (2012) Ascorbic acid: chemistry, biology and the treatment of cancer. Biochimica and Biophysica Acta. 1826: 443-457. doi: 10.1016/j.bbcan.2012.06.003.
16. Buettner GR (1993) The pecking order of free radicals, antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Archive of Biochemistry and Biophysics. 300 (2): 535-543. doi: 10.1006/abbi.1993.1074.
17. Cimmino L, Neel BG, Aifantis I (2018) Vitamin C in stem cell reprogramming and cancer. Trends in Cell Biology. 28: 698-708. doi: 10.1016/j.tcb.2018.04.001.
18. Will JC, Byers T (1996) Does diabetes mellitus increase the requirement for vitamin C? Nutrition Reviews. 54 (7): 193-202. doi: 10.1111/j.1753-4887.1996.tb03932.x.
19. Du WD, Yuan ZR, Sun J, Tang JX, Cheng AQ, Shen DM, Huang CJ, Song XH, Yu XF, Zheng SB (2003) Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms. World Journal of Gastroenterology. 9 (11): 2565-2569. doi:10.3748/wjg.v9.i11.2565.
20. Vural H, Uzun K (2000) Serum and red blood cell antioxidant status in patients with bronchial asthma. Canadian Respiratory Journal. 7 (6): 476-80. doi: 10.1155/2000/907478.
21. Vita JA, Keaney JF, Raby KE, Morrow JD, Freedman JE, Lynch S, Koulouris SN, Hankin BR, Frei B (1998) Low plasma ascorbic acid independently predicts the presence of an unstable coronary syndrome. Journal of American College of Cardiology. 31 (5): 980-986.
22. Carr AC, Frei B (1999) Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. American Journal of Clinical Nutrition. 69 (6): 1086-1107. doi: 10.1093/ajcn/69.6.1086.
23. Berman R (2021) Vitamin C: Revisiting controversial study may change recommendations. Medical news today. www.medicalnewstoday.com/articles/vitamin-c-revisiting-controversial-study-may-change-recommendations
24. Amanda B, White N (2016) Vitamin C in the prevention and treatment of the common cold. American Journal of Lifestyle Medicine. 10 (3): 181-183. doi:10.1177/1559827616629092.
25. Kongerud J, Crissman K, Hatch G, Alexis N (2003) Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhalation Toxicology. 15 (2): 101-109. doi: 10.1080/08958370304477.
26. Hemilä H, Chalker E (2013) Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 1:CD000980. doi:10.1002/14651858.CD000980.
27. Joshipura KJ, Hu FB, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Colditz G, Ascherio A, Rosner B, Spiegelman D, Willett W C (2001) The effect of fruit and vegetable intake on risk for coronary heart disease. Annals of Internal Medicine. 134: 1106-1114. doi: 10.7326/0003-4819-134-12-200106190-00010.
28. Nilsson TK, Sundell IB, Hellsten G, Hallmans G (1990) Reduced plasminogen activator inhibitor activity in high consumers of

fruits, vegetables and root vegetables. Journal of Internal Medicine. 227 (4): 267-271. org/10.1111/j.1365-2796.1990.tb00156.x.
29. Bordia AK (1980) The effect of vitamin C on blood lipids, fibrinolytic activity, platelet adhesiveness in patients with coronary artery disease. Atherosclerosis. 35 (2): 181-187. doi: 10.1016/0021-9150(80)90083-0.
30. Duffy SJ, Gokce N, Holbrook M, Huang A, Frei B, Keaney JF, Vita JA (1999) Treatment of hypertension with ascorbic acid. Lancet. 354 (9195): 2048-2049. doi: 10.1016/s0140-6736(99)04410-4.
31. Moran JP, Cohen L, Greene JM, Xu G, Feldman EB, Hames CG, Feldman DS (1993) Plasma ascorbic acid concentrations relate inversely to blood pressure in human subjects. American Journal of Clinical Nutrition. 57: 213-217. doi: 10.1093/ajcn/57.2.213.
32. Bates CJ, Walmsley CM, Prentice A, Finch S (1998) Does vitamin C reduce blood pressure? Results of a large study of people aged 65 or older. Journal of Hypertension. 16 (7): 925-932. doi: 10.1097/00004872-199816070-00005.
33. Mak S, Egri Z, Tanna G, Colman R, Newton GE (2002) Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. American Journal of Physiology. Heart and Circulatory Physiology. 282 (6): H2414-2421. doi: 10.1152/ajpheart.00947.2001.
34. Bayerle-Eder M, Pleiner J, Mittermayer F, Schaller G, Roden M, Waldhausl W, Bieglmayer C, Wolzt M (2004) Effect of systemic vitamin C on free fatty acid-induced lipid peroxidation. Diabetes and Metabolism. 30 (5): 433-439. doi: 10.1016/s1262-3636(07)70140-4.
35. Aburawi SM, Ben Saad JM, Al-Tubuly RA, Eldrogi AE (2007) Acute effect of ascorbic acid and alprazolam on behaviour, skeletal muscle activity and brain glutamate levels in Albino rats. FIP 31/8-6/9, 2007 Beijing, China.
36. Sullivan DR (2002) Screening for cardiovascular disease with cholesterol. Clinica Chimica Acta. 315 (1-2): 49-60. doi: 10.1016/s0009-8981(01)00720-3.
37. Stringer MD, Gorog PG, Freeman A, Kakkar VV (1989) Lipid peroxides and atherosclerosis. British Medical Journal. 298: 281-284. doi.org/10.1136/bmj.298.6669.281.
38. Diaz MN, Frei B, Vita JA, Keaney JF (1997) Antioxidants and atherosclerotic heart disease. New England Journal of Medicine. 337: 408-416. doi: 10.1056/NEJM199708073370607
39. Abuja PM (1999) Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. FEBS Letters. 446 (2-3): 305-308. doi: 10.1016/s0014-5793(99)00231-8.
40. Lehr HA, Frei B, Olofsson AM, Carew TE, Arfors KE (1995) Protection from oxidized LDL-induced leukocyte adhesion to microvascular and macrovascular endothelium in vivo by vitamin C but not by vitamin E. Circulation. 91 (5): 1525-1532. doi.org/10.1161/01.CIR.91.5.1525
41. Alosta IM (2008) The effect of ascorbic acid on hypertensive patients and their lipid profile: a prospective clinical study. Zwied OA, Al-Tubuly RA, El-Tomi AM. M. Sc thesis. Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Al-Fateh Medical University. Tripoli, Libya.
42. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Welsh-Bohmer KA, Breitner JCS (2004) Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache county study. Archives of Neurology. 61 (1): 82-88. doi: 10.1001/archneur.61.1.82.
43. Dakhale G, Khanzode S, Khanzode S, Saoji A, Khobragade L, Turankar A (2004) Oxidative damage and schizophrenia: the potential benefit by atypical antipsychotics. Neuropsychobiology. 49: 205-209. doi: 10.1159/000077368.
44. Abdalla DS, Monteiro HP, Oliveira JA, Bechara EJ (1986) Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. Clinical Chemistry. 32 (5): 805-807. PMID: 2870827.
45. Kuloghi M, Ustundag B, Atmaca M, Canatan H, Tezean AE, Cinkiline N (2002) Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochemistry and Function. 20: 171-175. doi: 10.1002/cbf.940.
46. Mahadik SP, Mukherjee S, Correnti I, Mahadik JS (1998) Elevated plasma lipid peroxidase at the onset of nonaffective psychosis. Biological Psychiatric. 43 (9): 674-679. doi: 10.1016/s0006-3223(97)00282-5.
47. Arvindakshan M, Sitasawad S, Debsikdar V, Ghate M, Evans D, Horrobin DF, Bennett C, Ranjekar PK, Mahadik SP (2003) Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenia patients. Biological Psychiatry. 53: 56-64. doi: 10.1016/s0006-3223(02)01443-9.
48. Gaur N, Gautam S, Gaur M, Sharma P, Dadheech G, Mishra S (2008) The biochemical womb of schizophrenia: a review. Indian Journal of Clinical Biochemistry. 23 (4): 307-327. doi: 10.1007/s12291-008-0071-x.
49. Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP (2003) Supplementation with a combination of omega 3 fatty acids and antioxidants (vitamin E and C) improves the outcome of schizophrenia. Schizophrenia Research. 62: 195-204. doi: 10.1016/s0920-9964(02)00284-0.
50. Dadheech G, Mishra S, Gautam S, Sharma P (2006) Oxidative stress-tocopherol, ascorbic acid and reduced glutathione status in schizophrenics. Indian Journal of Clinical Biochemistry. 21 (2): 34-38. PMCID: PMC3453982.
51. Aburawi SM, Ghambirlou FA, Attumi AA, Altubuly RA, Kara AA (2014) Effect of ascorbic acid on mental depression drug therapy: clinical study. Journal of Psychology Psychotherapy. 4: 131. doi.org/10.4172/2161-0487.1000131.
52. Martindale JL, Holbrook NJ (2002) Cellular response to oxidative stress: Signaling for suicide and survival. Journal of Cellular Physiology. 192: 1-15. doi: 10.1002/jcp.10119.
53. Bae YS, Oh H, Rhee SG, Yoo Y (2011) Do Regulation of reactive oxygen species generation in cell signaling. Molecules and Cells. 32: 491-509. doi: 10.1007/s10059-011-0276-3.
54. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010) Oxidative stress, inflammation, and cancer: How are they linked? Free Radical Biology and Medicine. 49: 1603-1616. doi: 10.1016/j.freeradbiomed.2010.09.006.
55. Zhao H, Zhu H, Huang J, Zhu Y, Hong M, Zhu H, Zhang JL, Yang L, Lian Y, Wang Shuai, Mao Jianping, Chen Y, Li J, Qian S (2018) The synergy of vitamin C with decitabine activates TET2 in leukemic cells and significantly improves overall survival in elderly patients with acute myeloid leukemia. Leukemia Research. 66: 1-7. doi: 10.1016/j.leukres.2017.12.009.
56. Cameron E, Pauling L (1976) Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. Proceedings of the National Academy of Sciences. 73: 3685-3689. doi: 10.1073/pnas.73.10.3685.
57. Cameron E, Pauling L (1978) Supplemental ascorbate in the supportive treatment of cancer: re-evaluation of prolongation of survival times in terminal human cancer. Proceedings of the National Academy of Sciences of the United States of America. 75: 4538-4542. doi: 10.1073/pnas.75.9.4538.
58. Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M (2004) Vitamin C pharmacokinetics: implications for oral and intravenous use. Annual of International Medicine. 140 (7): 533-537. doi: 10.7326/0003-4819-140-7-200404060-00010.
59. Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter Emily, Levine M (2005) Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. Proceedings of the National Academy of Sciences. 102 (38): 13604-9. doi.org/10.1073/pnas.0506390102.
60. Sakagami H, Satoh K, Hakeda Y, Kumegawa M (2000) Apoptosis-inducing activity of vitamin C and vitamin K. Cellular and Molecular Biology. 46:129-143. PMID: 10726979.
61. Kathleen A (1998) Ascorbic acid in prevention and treatment of cancer. Alternative Medicine Review. 3 (3): 174-186. PMID: 9630735.
62. Cabanillas F (2010) Vitamin C and cancer: what can we conclude-1, 609 patients and 33 years later? Puerto Rico Health Sciences Journal. 29 (3): 215-217. PMID: 20799507.

63. Chen, Q, Espey MG, Sun AY, Pooput C, Kirk KL, Krishna MC, Khosh DB, Drisko J, Levine M (2008) Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. Proceedings of the National Academy of the Sciences of the United State of America. 105: 11105-11109. doi: 10.1073/pnas.0804226105.
64. Padayatty SJ, Levine M (2016) Vitamin C: the known and the unknown and Goldilocks. Oral Diseases. 22 (6): 463-493. doi:10.1111/odi.12446.
65. Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C (2008) Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. International Journal of Cancer. 123: 1227-1239. doi: 10.1002/ijc.23754.
66. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, Friesen M, Tjønneland A, Olsen A, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Touvier M, Boeing H, Schulz M, Linseisen J, Nagel G, Trichopoulou A, Naska A, Oikonomou E, Krogh V, Panico S, Masala G, Sacerdote C, Tumino R, Peeters PH, Numans ME, Bueno-de-Mesquita HB, Büchner FL, Lund E, Pera G, Sanchez CN, Sánchez MJ, Arriola L, Barricarte A, Quirós JR, Hallmans G, Stenling R, Berglund G, Bingham S, Khaw KT, Key T, Allen N, Carneiro F, Mahlke U, Del Giudice G, Palli D, Kaaks R, Gonzalez CA (2006) Plasma and dietary vitamin C levels and risk of gastric cancer in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). Carcinogenesis. 27 (11): 2250-2257. doi: 10.1093/carcin/bgl096.
67. Naidu AK, Karl RC, Naidu KA, Coppola D (2003) The antiproliferative and pro-apoptotic effect of Ascorbyl Stearate in Human pancreatic cancer cells: Association with decreased expression of insulin-like growth factor receptor-1. Digestive Disease and Sciences. 48 (1): 230-237. doi: 10.1023/a:1021779624971.
68. Semenza G (2003) Targeting HIF-1 for cancer therapy. Nature Reviews Cancer. 3: 721-732. doi.org/10.1038/nrc1187.
69. Gao P, Zhang H, Dinavahi R, Li F, Xiang Y, Raman V, Bhujwalla ZM, Felsher DW, Cheng L, Pevsner J, Linda A, Gregg L, Semenza L, Dang CV (2007) HIF-dependent antitumorigenic effect of antioxidants in vivo. Cancer Cell. 12: 230-238. doi: 10.1016/j.ccr.2007.08.004.
70. Zambrano A, Molt M, Uribe E, Salas M (2019) Glut 1 in cancer cells and the inhibitory action of resveratrol as a potential therapeutic strategy. International Journal of Molecular Sciences. 20 (13): 3374. doi.org/10.3390/ijms20133374.
71. Rasmussen KD, Helin K (2016) Role of TET enzymes in DNA methylation, development, and cancer. Genes and Development. 30 (7): 733-750. doi.org/10.1101/gad.276568.115.
72. Bonnefont-Rousselot D (2004) The role of antioxidant micronutrients in the prevention of diabetic complications. Treatments in Endocrinology. 3 (1): 41-52. doi: 10.2165/00024677-200403010-00005.
73. Colagar AH, Marzony ET (2009) Ascorbic acid in human seminal plasma: determination and its relationship to sperm quality. Journal of Clinical Biochemistry and Nutrition. 45 (2): 144-149. doi: 10.3164/jcbn.08-251.
74. Agarwal A, Ikemoto I, Loughlin KR (1994) Relationship of sperm parameters to levels of reactive oxygen species in semen specimens. Journal of Urology. 152: 107-110.
75. Shukla KK, Mahdi AA, Ahmad MK, Jaiswar SP, Shankwar SN, Tiwari SC (2010) Mucuna pruriens reduces stress and improves the quality of semen in infertile men. Evidence-Based Complementary Alternative Medicine. 7 (1): 137-144. doi: 10.1093/ecam/nem171.
76. Aitken RJ, Baker MA (2006) Oxidative stress, sperm survival and fertility control. Molecular and Cellular Endocrinology. 250: 66-69. doi: 10.1016/j.mce.2005.12.026.
77. Sapra MM, Sharma PP, Kothari LK (1987) Effect of vitamin C deficiency on testicular structure in guinea pig. Journal of Postgraduate Medicine. 33: 69-73. PMID: 3681751.
78. Angulo C, Maldonado R, Pulgar E, Mancilla H, Córdova A, Villarroel F, Castro MA, Concha II (2011). Vitamin C and oxidative stress in the seminiferous epithelium. Biological Research. 44 (2): 169-180. doi.org/10.4067/S0716-97602011000200009.
79. Verma A, Kanwar KC (1998) Human sperm motility and lipid peroxidation in different ascorbic acid concentrations: an invitro analysis. Andrologia. 30: 325-329. doi: 10.1111/j.1439-0272.1998.tb01178.x.
80. Henmi H, Endo T, Kitaiima Y, Manase K, Hata H, Kudo R (2002) Effects of ascorbic acid supplementation on serum progesterone levels in patients with a luteal phase defect. Fertilely and Sterility. 80: 459-461. doi: 10.1016/s0015-0282(03)00657-5.
81. Jelodar G, Nazifi S, Akbari A (2013) The prophylactic effect of vitamin C on induced oxidative stress in rat testis following exposure to 900 MHz radio frequency wave generated by a BTS antenna model. Electromagnetic Biology and Medicine. 32 (3): 409-416. doi:10.3109/15368378.2012.735208.
82. Donnelly E, McClure N, Lewis SEM (1999) The effect of ascorbate and alpha-tocopherol supplementation in vitro on DNA integrity and hydrogen peroxide induced DNA damage in human spermatozoa. Mutagenesis. 14: 505-512. doi: 10.1093/mutage/14.5.505.
83. Kodama H, Yamaguchi R, Fukuda J, Kasi H, Tanaka K (1997) Increased oxidative deoxyribonucleic acid damage in spermatozoa of infertile male patients. Fertility and Sterility. 68: 519-524. doi: 10.1016/s0015-0282(97)00236-7.
84. Treesh SA, Aburawi SM, Elghedamsi MT, El Jaafari HA, Alzowam R, Shibani N, Khair NS (2019) Protective role of vitamin C on histopathological effect of formaldehyde on reproductive system in female albino mice (histological study). International Journal of Advanced Research. 7 (2): 529 - 540. doi.org/10.5281/zenodo.259001.
85. Stocker R, Keaney JF (2004) Role of oxidative modifications in atherosclerosis. Physiological Reviews. 84 (4): 1381-478. doi: 10.1152/physrev.00047.2003.
86. Lehr HA, Frei B, Arfors KE (1994) Vitamin C prevents cigarette smoke-induced leukocyte aggregation and adhesion to endothelium in vivo. Proceedings of the National Academy of Sciences. 91: 7688-7692. doi: 10.1073/pnas.91.16.7688.
87. Valkonen MM, Kuusi T (2000) Vitamin C prevents the acute atherogenic effects of passive smoking. Free Radical Biology and Medicine. 28 (3): 3-428-436. doi: 10.1016/s0891-5849(99)00260-9.
88. Kothari LK, Sharma P (1988) Aggravation of cholesterol induced hyperlipidemia by chronic vitamin C deficiency: experimental study in guinea pigs. Acta Biologica Hungarica. 39 (1): 49-57. PMID: 3254010.
89. Gale CR, Martyn CN, Winter PD, Cooper C (1995) Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. British Medical Journal. 310: 1563-1566. doi: 10.1136/bmj.310.6994.1563.
90. Enstrom JE, Kanim LE, Klein MA (1992) Vitamin C intake and mortality among a sample of the United States population. Epidemiology. 3: 194-202. doi: 10.1097/00001648-199205000-00003.
91. McRae MP (2008) Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials. Journal of Chiropractic Medicine. 7 (2): 48-58. doi: 10.1016/j.jcme.2008.01.002.
92. Feigen GA, Smith BH, Dix CE, Flynn CJ, Peterson NS, Rosenberg LT, Pavlović S, Leibovitz B (1982) Enhancement of antibody production and protection against systemic anaphylaxis by large doses of vitamin C. Research Communication of Chemical Pathology and Pharmacology. 38 (2): 313-33. PMID: 7163630.
93. Wintergerst ES, Maggini S, Hornig DH (2006) Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Annals of Nutrition and Metabolism. 50 (2): 85-94. doi: 10.1159/000090495.
94. Mikirova N, Casciari J, Rogers A, Taylor P (2012) Effect of high-dose intravenous vitamin C on inflammation in cancer patients. Journal of Translational Medicine. 10: 189. doi: 10.1186/1479-5876-10-189.
95. Holmannová D, Koláčková M, Krejsek J (2012) Vitamin C and its physiological role with respect to the components of the immune

system. Vnitri Lekarstvi. 58 (10): 743-749. PMID: 23121060.
96. Aburawi SM, Alahmer NM, Eltaif NF, Altubuly RA, Sufya NM (2013) Effect of vitamin C on penicillin g efficacy to inhibit bacterial populations. Tripolitana Medical Journal. 2 (2): 44-49.
97. Bourne GH (1946) The effect of vitamin C on healing wounds. Proceedings of Nutrition Society. 4 (3-4): 204. doi: 10.1079/pns19460041.
98. Moores J (2013) Vitamin C: a wound healing perspective. British Journal of Community Nursing. S6, S8-11. doi: 10.12968/bjcn.2013.18. sup12.s6.
99. Ringsdorf WM, Cheraskin E (1982) Vitamin C and human wound healing. Oral Surgery Oral Medicine Oral Pathology Oral Radiology. 53 (3): 231-236. doi: 10.1016/0030-4220(82)90295-x.
100. Chan PK, Cho HJ, Cho KH, Chung JH, Han KK, Lee IW, Song PI, Wha KS (2002) Fibroblasts and ascorbate regulate epidermalization in reconstructed human epidermis. Journal of Dermatological Science. 30 (3): 215-223. doi: 10.1016/s0923-1811(02)00108-1.
101. Sarisozen B, Durak K, Dincer G, Bilgen OF (2002) The effects of vitamins E and C on fracture healing in rats. The Journal of International Medical Research. 30 (3): 309-313. doi: 10.1177/147323000203000312.
102. Aburawi SM, Al Tubuly R, Friwan A, Al-Ghdamsi M (2017) screening for analgesic and anti-inflammatory effect of antioxidants by applying formalin test using albino mice. AlQalam Journal of Medical and Biological Research. 1 (1): 1-8. www.utripoli.edu.ly
103. Zeraati F, Araghchian M, Esna-Ashari F, Torabian S, Fallah N, Ghavimi M (2014) Antinociceptive properties of ascorbic acid: evidence for the mechanism of action. Avicenna Journal of Medical Biochemistry. 2 (1): 3. doi:10.17795/ajmb-18572.
104. Rosa KA, Gadotti VM, Rosa AO, Rodrigues AL, Calixto JB, Santos AR (2005). Evidence for the involvement of glutamatergic system in the antinociceptive effect of ascorbic acid. Neuroscience Letters. 381 (1-2): 185-188. doi: 10.1016/j.neulet.2005.02.032.
105. Lu R, Kallenborn-Gerhardt W, Geisslinger G, Schmidtko A (2011) Additive antinociceptive effects of a combination of vitamin C and vitamin E after peripheral nerve injury. PLoS ONE. 6 (12): e29240. doi: 10.1371/journal.pone.0029240.
106. Simon JA, Hudes ES (1999) Serum ascorbic acid and other correlates of self-reported cataract among older Americans. Journal of Clinical Epidemiology. 52 (12): 1207-1211. doi: 10.1016/s0895-4356(99)00110-9.
107. Marino S (2015) Iron and vitamin C: the perfect pair? Michigan State University, MSU Extension, Colleen Kokx, Dietetic Intern - February 13, 2015.
108. Chiu PF, Ko SY, Chang CC (2012) Vitamin C affects the expression of hepcidin and erythropoietin receptor in HepG2 cells. Journal of Renal Nutrition. 22 (3): 373-376. doi: 10.1053/j.jrn.2011.09.007.
109. Alessia P, Antonella N, Laura S, Clara C (2019) Hepcidin and Anemia: a tight relationship. Frontiers in Physiology. 10: 1294. doi: 10.3389/fphys.2019.01294.
110. Lane D, Chikhani S, Richardson V, Richardson DR (2013) Transferrin iron uptake is stimulated by ascorbate via an intracellular reductive mechanism. Biochimica et Biophysica Acta. 1833 (6): 1527-1541. doi: 10.1016/j.bbamcr.2013.02.010.
111. Foronjy R, D'Armiento J (2006) The Effect of Cigarette Smoke-derived Oxidants on the Inflammatory Response of the Lung. Clinical and Applied Immunology Reviews. 6 (1): 53-72. doi:10.1016/j.cair.2006.04.002.
112. Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, Ames BN (2000) Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes, The American Journal of Clinical Nutrition. 71 (2): 530-536. doi.org/10.1093/ajcn/71.2.530.
113. Esen AM, Barutcu I, Acar M, Degirmenci B, Kaya D, Turkmen M, Melek M, Onrat E, Esen OB, Kirma C (2004) Effect of smoking on endothelial function and wall thickness of brachial artery. Circulation Journal. 68 (12): 1123-6. doi: 10.1253/circj.68.1123.
114. Kaufmann PA, Gnecchi-Ruscone T, di Terlizzi M, Schäfers KP, Lüscher TF, Camici PG (2000) Coronary heart disease in smokers: vitamin C restores coronary microcirculatory function. Circulation. 102 (11): 1233-8. doi: 10.1161/01.cir.102.11.1233.
115. Ames BN (2001) DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. Mutation Research. 475 (1-2): 7-20. doi: 10.1016/s0027-5107(01)00070-7.
116. Mastrangelo D, Pelosi E, Castelli G, Lo-Coco F, Testa U (2018) Mechanisms of anti-cancer effects of ascorbate: cytotoxic activity and epigenetic modulation. Blood Cells, Molecules and Diseases. 69: 57-64. doi: 10.1016/j.bcmd.2017.09.005.
117. Pawlowska E, Szczepanska J, Blasiak J (2019) Pro- and antioxidant effects of vitamin c in cancer in correspondence to its dietary and pharmacological concentrations. Oxidative Medicine and Cellular Longevity. 18. doi.org/10.1155/2019/7286737.
118. National Academic Press (2000) Panel on dietary antioxidants and related compounds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. ISBN-10: 0-309-06935-1.
119. Knight J, Madduma-Liyanage K, Mobley JA, Assimos DG, Holmes RP (2016) Ascorbic acid intake and oxalate synthesis. Urolithiasis. 44: 289-297. doi: 10.1007/s00240-016-0868-7.
120. Lin WV, Turin CG, McCormick DW, Haas C, Constantine G (2019) Ascorbic acid-induced oxalate nephropathy: a case report and discussion of pathologic mechanisms. Clinical and Experimental Nephrology Case Reports. 8: 67-70. doi: 10.1007/s13730-018-0366-6.
121. Honore PM, Spapen HD, Marik P, Boer W, Oudemans-van Straaten H (2020) Dosing vitamin C in critically ill patients with special attention to renal replacement therapy: a narrative review. Annual of Intensive Care. 12, 10 (1): 23. doi: 10.1186/s13613-020-0640-6.
122. Gurm H, Sheta MA, Nivera N, Tunkel A (2012) Vitamin C-induced oxalate nephropathy: a case report. Journal of Community Hospital Internal Medicine Perspectives. 2 (2): 17718. doi:10.3402/jchimp.v2i2.17718.
123. El-Sokkary GH, Awadalla EA (2011) The protective role of vitamin C against cerebral and pulmonary damage induced by cadmium chloride in male adult albino rat. The Open Neuroendocrinology Journal. 4: 1-8.
124. Hounkpatin ASY, Johnson RC, Guédénon P, Domingo E, Alimba CG, Boko M (2012) Protective effects of vitamin C on haematological parameters in intoxicated Wistar rats with cadmium, mercury and combined cadmium and mercury. International Research Journal of Biology and Sciences. 1 (8): 76-81.
125. Gajawat S, Sancheti G, Goyal PK (2005) Vitamin C against concomitant exposure to heavy metal and radiation: a study on variations in hepatic cellular counts. Asian Journal of Experimental Sciences. 19 (2): 53-58.
126. Shaban EM, Said EY (2011) Influence of vitamin C supplementation on lead-induced histopathological alterations in male rats. Experimental and Toxicologic Pathology. 63 (3): 221-227. doi: 10.1016/j.etp.2009.12.003.
127. Kosik-Bogacka DI, Baranowska-Bosiacka I, Marchlewicz M, Kolasa A, Jakubowska K, Olszewska M, Łanocha N, Wiernicki I, Millo B, Wiszniewska B, Chlubek D (2011) The effect of L-ascorbic acid and/or tocopherol supplementation on electrophysiological parameters of the colon of rats chronically exposed to lead. Medical science monitor: International Medical Journal of Experimental and Clinical Research. 17 (1): BR16–BR26. doi.org/10.12659/msm.881323.
128. Singh AL, Singh VK, Srivastava A (2013) Effect of arsenic contaminated drinking water on human chromosome: a case study. Indian Journal of Clinical Biochemistry. 28: 422-425. doi: 10.1007/s12291-013-0330-3.
129. Herrera A, Pineda J, Antonio MT (2013) Toxic effects of perinatal arsenic exposure on the brain of developing rats and the beneficial role of natural antioxidants. Environmental Toxicology and Pharmacology. 36 (1): 73-79. doi: 10.1016/j.etap.2013.03.018.
130. Singh S, Rana SV (2010) Ascorbic acid improves mitochondrial function in liver of arsenic-treated rat. Toxicological and Industrial Health. 26 (5): 265-272. doi: org/10.1177/0748233710365694.

131. Aburawi SM (2016) Mental depression drug therapy in presence of ascorbic acid: clinical study. Dual Diagnosis: Open Access. 1: 12. doi: 10.21767/2472-5048.100012.
132. Aburawi SM, Doro BM, Awad EA (2019) Effect of Ciprofloxacin on S. aureus and E. coli growth in presence of vitamin c using cup cut diffusion method. Journal of Pharmacy and Pharmacology. 7: 473-484. doi: 10.17265/2328-2150/2019.08.003.
133. Aburawi SM, Owheda MA, Al-Jadid GA (2019) Effect of black tea preparation on vitamin C absorption in albino rat ileum using everted gut sac technique. Pharmacophore. 10 (6): 9-13.
134. Ben Saad JM, Eldrogi AF, Al-Tubuly RA, Aburawi SM (2016) Neurobehavioral effect of alprazolam in presence of ascorbic acid using albino rats. Lebda Medical Journal. 2: 68-82.
135. Aburawi SM, Eldrogi AE, Al-Tubuly RA, Ben Saad JM (2008) Interaction effects of alprazolam and ascorbic acid on behaviour and brain gaba levels in albino rats. Assiut University 6th International Pharmaceutical Science Conference, Faculty of Pharmacy, 12-13 March, 2008. Assiut, Egypt.
136. Aburawi SM, Saad SEM, Burawi EN, Alalem HE (2021) Behavioural effects of vitamin C with haloperidol in mice. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 1 (3): 46-55. doi.org/10.5281/zenodo.5534626.
137. de Carvalho Melo-Cavalcante AA, da Rocha Sousa L, Alencar MVOB, de Oliveira Santos JV, da Mata AMO, Paz MFCJ, de Carvalho RM, Nunes NMF, Islam MT, Mendes AN, Gonçalves JCR, da Silva FCC, Ferreira PMP, de Castro E Sousaa JM (2019) Retinol palmitate and ascorbic acid: Role in oncological prevention and therapy. Biomedical Pharmacotherapy. 109: 1394-1405. doi: 10.1016/j.biopha.2018.10.115.
138. McRae MP (2006) The efficacy of vitamin C supplementation on reducing total serum cholesterol in human subjects: a review and analysis of 51 experimental trials. Journal of Chiropractic Medicine. 5 (1): 2-12. doi: 10.1016/S0899-3467(07)60127-X.
139. Itoh R, Yamada K, Oka J, Echizen H, Suyama Y, Murakami K (1990) Serum ascorbic acid and HDL cholesterol in a healthy elderly Japanese population. International Journal of Vitamin and Nutrition Research. 60 (4): 360-365. PMID: 2101828.
140. Gautam M, Agrawal M, Gautam M, Sharma P, Gautam AS, Gautam S (2012) Role of antioxidants in generalised anxiety disorder and depression. Indian Journal of Psychiatry. 54 (3): 244-247. doi: 10.4103/0019-5545.102424.
141. Harrison FE (2012) A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. Journal of Alzheimer's Disease. 29 (4): 711-726. doi: 10.3233/JAD-2012-111853.