

Vitamin C: optimal dosages, supplementation and use in disease prevention

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Submission date: February 4, 2015; Acceptance date: March 5, 2015, Publication date: March 7, 2015

ABSTRACT:

The importance of vitamin C as a way to prevent scurvy has been known for centuries. More recent research on vitamin C has expanded beyond scurvy prevention, providing promising evidence for additional health benefits and clinical applications. This review of scientific literature will evaluate many aspects of vitamin C, including deficient versus optimal blood plasma levels, adequate daily amounts necessary to maintain ideal levels, and the safety of higher doses. It will also focus on the importance of vitamin C as a powerful bioactive compound, and its use towards the prevention and management of different chronic diseases. This review is necessary to express the importance of alternative healthcare methods in both preventative and clinical care. Vitamin C was chosen as a representative of this concept, mainly due to its powerful antioxidant capacity, incredibly important physiological implications, and very minimal chance of side-effects. This review focuses on studies involving human participants that address how vitamin C is important for our health.

Keywords: Ascorbic acid, deficiency, disease, dose, health, supplementation, vitamin C

INTRODUCTION:

Vitamin C was first identified in fruits (citrus), vegetables and adrenal glands as hexuronic acid in the 1920s by Albert Szent-Györgyi, a Hungarian biochemist. With the help of an American physician named Joseph Svibely, Szent-Györgyi was able to identify that hexuronic acid was vitamin C through scurvy research on guinea pigs. It was later named ascorbic acid (meaning “without scurvy” from Latin) by Szent-Györgyi and Norman Haworth, a scientist who also studied vitamin C [1].

Vitamin C is a crucial component to human health. This particular vitamin is water soluble (causing quick elimination and preventing storage) and cannot be synthesized by humans; therefore, it is essential that vitamin C be incorporated into our diet [2]. The particular mechanism that prevents synthesis is the absence of gulonolactone oxidase (GLO) [3], which is necessary to catalyze the enzyme L-gulonolactone oxidase, the final step in the biosynthetic pathway of vitamin C [4]. There are numerous reasons why vitamin C is important to our health,

but many relate to how it is essential for the synthesis of collagen, carnitine and norepinephrine [5].

The two main components of vitamin C are ascorbate and dehydroascorbic acid (DHA) [3]. The transport of ascorbate through the human body involves two sodium-dependent vitamin C transporters (SVCT): SVCT1 and SVCT2 [6]. The majority of ascorbate is transported by SVCT1 in epithelial cells (e.g. intestine, kidney and liver), and the remaining is transported by SVCT2 in specialized cells (e.g. brain and eye) [7]. DHA (the oxidized form of ascorbate) is transported in the human body through 2 glucose transporters (GLUT): GLUT1 and GLUT3 [6] (a third transporter, GLUT 4, is used only for insulin-sensitive tissues [8]). Once DHA has been transported inside the cell by a GLUT, it is reduced back to ascorbate [6]. The distribution and homeostasis of vitamin C in the human body is regulated by the SVCTs, GLUTs, facilitated diffusion through channels and exocytosis in secretory vesicles [9]. The main concentrations of vitamin C are located in brain and adrenal cells.

RETRIEVAL OF PUBLISHED STUDIES:

A systematic review of published studies concerning the importance of vitamin C for our health was conducted electronically using PubMed® and Google Scholar. Both review and research papers were included. Eligible articles provided reasonable, scientific evidence on the positive benefits of vitamin C for human health. Articles not available in English were excluded. Keywords for the search included: addict, antioxidant, ascorbic acid, content, cooking, deficiency, disease, dose, elderly, health, history, intake, iron, IV, oral, oxidant, physiological, plasma, pregnant, preparation, prevention, research, risk, safety, scurvy, storage, supplement, symptoms, treatment, and vitamin C.

VITAMIN C AS AN ANTIOXIDANT:

The importance of vitamin C stems from its powerful antioxidant capacity. The term antioxidant has been defined as, “any substance that, when present at low concentrations compared to those of an oxidisable substrate, significantly delays or prevents oxidation of that substrate” [10]. Out of the three different antioxidant defense systems, vitamin C is classified as a chain breaking antioxidant; specifically, an aqueous phase chain breaking antioxidant [11]. As an antioxidant, vitamin C protects low-density lipoproteins (LDLs) from being oxidized, decreases damaging oxidation in the stomach, and facilitates the absorption of iron [8].

In one study examining the chemical composition of broccoli and cauliflower, vitamin C was shown to have the highest positive correlation of phytochemicals (phenol, flavonoid and glucosinolate), and the second highest antioxidant activity (only 9.5% lower than total phenol) [12]. In another study highlighting the antioxidant capacity of jujube fruits, vitamin C had the highest correlation coefficient in the 2,2'-azinobis (3-ethylbenzothiazoline-6) sulfonic acid (ABTS) scavenging method (which establishes antioxidant activity) [13].

WHY VITAMIN C IS SO IMPORTANT TO HEALTH:

Vitamin C is crucial to our overall health and wellbeing. It should be considered a functional food ingredient, as it is an important bioactive compound with antioxidant properties. A functional food is defined as “natural or processed foods that contain known or unknown

biologically active compounds; which, in defined amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease” [14]. Those health benefits are numerous, and will be discussed further in a later section. One of its most important aspects involves its role in cognitive functions, due to its high concentration in the brain [15]. This affects us in different ways throughout our life. Concerning our early years, there is animal-model data that suggests vitamin C deficiency in newborns could result in impaired spatial memory, due to decreased neurons (~30% loss) in the hippocampus [16]. As we get older, the importance of an adequate amount of daily vitamin C over a lifetime could help prevent certain degenerative diseases. For example, vitamin C is a main defense against dopamine auto toxicity, a major component of Parkinson’s disease [17].

Physiological Role of Vitamin C

In a general sense, vitamin C acts as a cofactor and reduces certain enzymes by providing them with electrons, due to its chemical structure [8]. Those enzymes can react with biomolecules known as lipids, proteins and DNA, and cause harm. In order to help prevent this, vitamin C reduces oxygen species when lipid peroxidation is formed, reduces radical inhibitors in protein oxidation, and prevents nitrosamine formation to reduce DNA damage [18].

The role of vitamin C in health could be related to its recycling ability in the presence of microorganisms [19]. When microorganisms are present, the amount of vitamin C in neutrophils is 30 times higher than in neutrophils that do not have microorganisms [19]. This is important due to the ability of vitamin C to provide oxidant protection by scavenging excessive reactive oxygen species (ROS), which causes oxidant damage [19-20]. When more vitamin C is produced due to recycling, the ability to protect the body against damage is increased.

Another reason why vitamin C is important is due to its ability to facilitate proper iron levels. In one comparison study, individuals who consumed 247 mg of vitamin C daily had 35% higher iron absorption levels than those who consumed 51 mg of vitamin C daily [21].

VITAMIN C DEFICIENCY – INDIVIDUALS AT RISK:

One reason for this review is the high prevalence of vitamin C deficient individuals. There is a strong correlation that individuals who smoke tobacco are at risk to be deficient in vitamin C [22]. This has been demonstrated by the United States Department of Agriculture (USDA), which specifies on their Recommended Dietary Allowances (RDA) that smokers require an additional 35 mg of vitamin C daily to maintain adequate levels [23]. One reason for this association is that smokers tend to consume a less healthy diet (specifically less fruits and vegetables) [24], leading to a 16% decrease in vitamin C intake [25]. Another reason is that cigarette smoke causes vitamin C to be depleted at a much faster rate, in order to compensate for the oxidative stress [25]. In one study conducted, ascorbate was completely depleted from human plasma after six puffs of cigarette smoke [26].

There is also an association between lower-income households and vitamin C deficiency. In the United Kingdom, a study was conducted on the 15% lowest income households to determine plasma vitamin C levels [27]. The results indicated that 26% of men and 16% of women were vitamin C deficient (<11 μmol), and 21% of men and 18% of women had depleted vitamin C levels (11–28 μmol) [27]. A main reason for this is that households with lower socioeconomic

status tend to consume less fruits and vegetables, which are essential sources of vitamin C. In one study, it was shown that 53% of low-income households spend less than \$1.00 a week on fresh fruit and vegetables [28].

Individuals who have more stressful lives (thereby creating more oxidative damage) are at risk for low vitamin C levels. Vitamin C decreases more quickly with increased oxidative stress, so higher intakes can help to better manage the increased emotional/physical pressure. It has been shown that helicopter pilots have a more stressful job compared to non-flight staff, based on serum levels of stress indicators, with 21.1% higher malondialdehyde (MDA), 21.7% higher superoxide dismutase (SOD), and 25.1% higher total antioxidant capacity (TAC) [29]. There are also issues of oxidative stress which result from a worker's environment, and not necessarily the job itself. Workers who have been exposed to lead (73 µg of lead/dl of blood) compared to those who haven't (6.7 µg of lead/dl) show a 46.2% higher thiobarbituric acid reactive species concentration (TBARS (nmol MDA/ml PG)), 60.9% higher SOD, 70.3% higher chloramphenicol acetyltransferase (CAT) activity, and a 40% higher TAC [30]. When these lead-exposed workers were given daily oral 1 g vitamin C supplements (in addition to 400 IU vitamin E) for one year, their TBARS decreased by 46.2%, TAC decreased by 36.4%, CAT decreased by 59.5%, and SOD decreased by 48.5%, bringing them back down to levels of their non-lead exposed workers [30].

Elderly individuals are at risk for malnutrition from multiple factors, including disease, medications, diminished senses (taste/smell), physical limitations (reaching/bending), depression, oral issues (difficulty chewing/swallowing, mouth pain, tooth loss, poorly fit dentures), financial issues, and stress (death of a loved one) [31]. An insufficient amount of calories also leads to diminished nutrients, such as vitamin C. In one study of over 400 community-dwelling elders (mean age of 76.8) with varying diets, the average intake of vitamin C was 55.57 mg [32], which is 25.9% lower than the RDA for women and 38.3% lower than the RDA for men.

Another group of individuals who are at risk include those who suffer from certain addictions. It has been shown that increased alcohol consumption leads to a decrease in plasma vitamin C due to the action of ethanol and/or poor diet: low drinkers (~10.6 g/d) have 41.4 µmol/L, moderate drinkers (~59 g/d) have 32.4 µmol/L, and alcoholics (~194.3 g/d) have 24.2 µmol/L [33]. This relationship has also been demonstrated in heroin addicts, where increased use led to a further decrease in vitamin C levels [34]. In another study, various drug addicts were shown to have a 43.6% lower vitamin C level than control subjects [35].

Women who are pregnant are also at risk for vitamin C deficiency, due to increased oxidative stress [36]. Pregnant women who are obese (BMI >30 kg m⁻²) have a greater risk of low vitamin C levels than pregnant women of a healthy weight (BMI 18–25 kg m⁻²), because their oxidative stress has been shown to be greater [37]. Low vitamin C levels during pregnancy can lead to various health issues to the fetus, such as low birth weight [36]. Many women take iron supplements during pregnancy, which have been shown to decrease vitamin C levels. In one study, pregnant women who were taking iron supplements had a 24% decrease in vitamin C levels from the 1st to the 3rd trimester, while women who were not taking iron supplements only had a 3.7% loss [38].

Individuals who are being treated in hospitals may also suffer from vitamin C deficiency. This is especially true for maintenance haemodialysis (MHD) patients. One study determined that 44.1% of MHD patients are vitamin C deficient with $<2 \mu\text{g/mL}$ (or $<11 \mu\text{mol/L}$) [39]. This is due to multiple factors, one being that MHD patients need to avoid foods that are high in potassium in order to help prevent hyperkalemia. Potassium-rich foods tend to be high in vitamin C; therefore, a decrease in potassium also causes a decrease in vitamin C [39]. Another reason these patients are at risk is that each dialysis treatment they receive can remove an average of 66 mg of vitamin C from their plasma levels [40].

VITAMIN C DEFICIENCY – SYMPTOMS:

A person who has a normal intake of vitamin C will have plasma levels of $>28 \mu\text{mol/L}$ or 0.4-0.9 mg/dl [41-42]. An individual with depleted vitamin C will have plasma levels between 11–28 $\mu\text{mol/L}$ or 0.2-0.39 mg/dl [41-42]. In order for an individual to be deficient, their vitamin C plasma levels must be $<11 \mu\text{mol/L}$ or $<0.2 \text{ mg/dl}$ [41-42]. Though the human body is resilient, vitamin C is an essential and water-soluble nutrient that is quickly excreted. Vitamin C has a half-life of 16 days in our bloodstream; if ingestion of it stops completely, it will be eliminated within 35-40 days [43]. While blood plasma levels drop fairly quickly, the symptoms of deficiency take much longer to develop [44]. In order to prevent deficiency, humans must ingest 10 mg of vitamin C daily (this prevents deficiency, but does not provide enough to reach normal plasma levels) [45]. Unfortunately, one of the earliest symptoms is very non-specific: fatigue. This is because vitamin C is involved in the biosynthesis of carnitine, a compound essential for producing energy by transporting long-chain fatty acids into the mitochondria [46]. A plethora of symptoms in vitamin C deficiency are related to collagen, an essential element in tendon, cartilage, bone and skin function [47]. Vitamin C is required by proline hydroxylase and lysine hydroxylase (enzymes in procollagen biosynthesis), and a deficiency leads to unstable collagenous structures [46, 48]. This causes tooth loss, joint pain, bone and connective tissue disorders, poor wound healing and more specifically: bleeding, bruising, edema, hemorrhage, gingivitis, and corkscrew hairs [48-50].

VITAMIN C OVERDOSE – EFFECTS:

The side effects of normal vitamin C intake are very minor, if non-existent, because it is water soluble and quickly excreted [51]. There have been some reports of negative effects in larger doses; to help prevent negative side effects and overdose, the USDA set the upper tolerable limit (UL) for vitamin C at 2 g [23]. Gastrointestinal distress and diarrhea are the most common side effects, which have been shown in single oral doses of 5-10 g or greater than 2 g daily, with symptoms disappearing within 1-2 weeks [51-52]. However, there has been evidence to suggest there are a few more severe side effects with high-dose vitamin C. The most note-worthy is the production of calcium oxalate stones in patients with renal issues (though some healthy individuals can also produce excessive oxalate at doses greater than 1 g daily [53]). This is because vitamin C converts to oxalate during the elimination process, which can cause formation of stones at high doses. In a fairly recent study there was evidence to support limited, but still statistically significant, oxalate formation with high dose vitamin C. Both groups took an oral 1 g vitamin C supplement twice daily for 6 days (2 trials were completed); the healthy group

reported a 20% increase in oxalate, while the group with renal issues had a 33% increase [54]. This study helps explain the controversy of whether high dose vitamin C is dangerous or not. There are documented cases of oxalate stone formation in subjects with renal issues, but the incidence rate is low. While a majority of the data surrounding oxalate formation provides statistically significant findings, there are no clinically significant ones [55]. An additional concern deals with an overproduction of iron. Vitamin C increases iron absorption by helping to transport iron across the epithelium in the small intestine [15]. Though this is a beneficial effect in most cases, there is potential for an iron overload in some individuals with diseases such as hemochromatosis, sideroblastic anemia, beta-thalassemia major and sickle cell anemia [56-57].

OPTIMAL DAILY INTAKE:

As with most nutrients, there are always questions about optimal intake. This can vary dramatically when considering different factors of age, health, lifestyle and gender. In regards to determining a daily amount best suited for the general population, the most recent RDA has been calculated at 90 mg for men and 75 mg for women, daily [23]. Many researchers believe this amount is too low, and have conducted experiments and reviews to explain why a higher daily intake would better benefit our health (Table 1).

Table 1: Comparison of optimal vitamin C intake

Study/Organization	Recommended Intake (Healthy Adults)	Reasoning
USDA RDA (IOM, FNB, 2000 [23])	90 mg oral (men), 75 mg oral (women)	Meets nutrient requirements for 97-98% of the population; calculated from an EAR
Vitamin C depletion-repletion pharmacokinetic studies in 7 healthy inpatient volunteers by using 7 doses from 30-2500mg. (Levine et al., 1996 [59])	200 mg oral	Bioavailability was complete at 200 mg
The combined evidence from human metabolic, pharmacokinetic, and observational studies and Phase II RCTs. (Frei, Birlouez-Aragon, & Lykkesfeldt, 2012 [60])	200 mg oral	Maximizes the vitamin's potential health benefits with the least risk of inadequacy or adverse health effects.
15 healthy female inpatients received in succession daily vitamin C doses of 30, 60, 100, 200, 400, 1,000, and 2,500 mg. (Levine, Wang, Padayatty, & Morrow, 2001 [58])	90 mg oral (women)	Using FNB guidelines and on the basis of determination of an EAR; produces a median of ≈80% vitamin C saturation of neutrophils; minimal urine excretion
Review of past findings, and analysis of recent findings, on optimal vitamin C dosage. (Ordman, 2010 [61])	500 mg oral twice daily	500 mg of vitamin C taken every 12 hrs may reduce many major causes of chronic disease, aging decline, and colds

In terms of gender, there is evidence to suggest that both men and women should have a RDA of 90 mg [58]. The RDA of 90 mg for men was calculated from depletion-repletion study data [59], and the RDA for women was calculated from the men’s dose by accounting for weight

differences (depletion-repletion study data was not available for women) [23]. Levine, Wang, Padayatty, and Morrow (2001) conducted their own depletion-repletion study specifically for women and determined that both sexes should have the same 90 mg daily intake, based off neutrophil saturation and urinary excretion [58]. Some studies and reviews have determined that 200 mg daily is the optimal intake [59-60], with others claiming that 1,000 mg (500 mg twice daily) provides the best health effects [61]. In terms of bioavailability, the absorption efficiency of vitamin C is 89% for 15 mg/day, 87% for 30 mg/day, 85% for 50 mg/day, 80% for 100 mg/day, 72% for 200 mg/day, 63% for 500 mg/day, and 46% for 1250 mg/day [62]. Although the higher intake is tolerated and absorbed to a certain extent, the maximum bioavailability seems to peak at 500 mg [51].

Though vitamin C tends to be well tolerated, even with high doses, maximum limits have been established. While the USDA has determined the UL for vitamin C at 2 g daily, the maximum tolerated *single* dose is 3 g [63], and the maximum tolerated *daily* dose is 18 g [64]. Those doses cannot be reached from food and beverage consumption; they must be administered through either oral supplementation or intravenous (IV) injection.

IV AND ORAL SUPPLEMENTATION:

Though vitamin C intake should primarily come from whole foods (to be discussed later), there are reasons to take either IV or oral supplements. Many individuals do not have access to foods high in vitamin C due to financial (e.g. high cost of produce) or physical (e.g. no local grocery store) limitations. Others may require more vitamin C due to a genetic predisposition, disease, or diet restriction [65]. Outside of trying to ensure a proper daily intake, another reason for taking supplements is for a pharmacologic effect in the treatment of diseases [65].

For individuals looking to ensure a proper daily intake of vitamin C, oral supplementation is efficient. In the clinical setting, however, IV dosing is more regularly used. This is because IV dosing of vitamin C produces a much higher plasma concentration than an oral dose. It has been shown that a 3 g oral dose produces a peak plasma concentration of 220 $\mu\text{mol/L}$, whereas a 3 g IV dose produces a peak plasma concentration of 1760 $\mu\text{mol/L}$ [63]. IV dosing also has the potential to increase peak plasma concentrations with an increased dose, whereas oral dosing eventually reaches a plateau in peak plasma concentration [63].

INCORPORATING VITAMIN C IN THE DIET:

Vitamin C is a crucial element to a healthy diet, and there are a number of ways to make sure we are ingesting an adequate daily amount. Though the chemical components of vitamin C supplements (oral/IV) and vitamin C in food are identical, the benefit of ingesting natural food-based vitamin C allows for the consumption of other important nutrients simultaneously [66]. This is important for both a balanced diet and for the increased health effects of certain nutrients. As mentioned earlier, vitamin C is able to help facilitate iron absorption [15, 21], so consuming foods rich in those nutrients together (i.e. a spinach salad topped with strawberries), would improve nutritional benefits. Another healthy combination is vitamin C and vitamin E, as they work together to inhibit oxidation [67]. Furthermore, vitamin C can help restore vitamin E levels by reducing α -tocopheroxyl (vitamin E radical) back to vitamin E [67]. Multiple studies have also shown that there is either little difference (in terms of plasma levels and urinary excretion)

between supplemental and food-based vitamin C, or that food-based vitamin C provides better absorption than supplements [68-70]. With the benefit of symbiotic nutrient relationships and similar/better reactions to that of supplements, food-based vitamin C may be the best choice for healthy individuals to obtain their daily requirement.

In order to ensure that individuals are getting the most vitamin C in their diet, there are a few items to consider. One concerns the area in which individuals live, and the availability of produce. In areas with limited produce due to the climate, individuals can attain vitamin C from herbs and organ meats [15]. If people live in an area without a fresh or even frozen produce section in their local market, they will be limited to canned fruits and vegetables, which have a much lower vitamin C content [5]. Even orange juice (the most frequently purchased vitamin C rich food [71]) tends to be an inadequate source. At 4 weeks before expiration, orange juice may only have ~75% of the vitamin C claimed on the nutrition label, and it degrades by ~2% every day after it is opened, leading to ~25% at expiration [72]. In these situations, the best method would be to purchase canned fruits and vegetables that have the highest vitamin C content, and to choose the latest expiration date on juices rich in vitamin C, consuming them promptly after purchasing.

Even when individuals do have access to fresh fruits and vegetables, there are many factors which can degrade vitamin C content. Preparation of foods is one factor that can make a huge difference. Boiling tends to degrade the vitamin C content of vegetables, with an average of 50.9% loss in common vegetables (table 2) [73-77]. This evidence is further shown in a recent randomized double-blind placebo control study. The 2 test groups both consumed 350 g of vegetables daily. Group A cooked the food using specialized cookware that did not require the use of excess water, while group B cooked the food using standard methods (i.e. boiling). In just 2 weeks, the blood vitamin C levels in group A increased by ~17%, whereas group B only increased by ~9% [78]. As shown by that study, cooking vegetables without the use of excess water can help to preserve vitamin C content. Stir frying is one method, which shows a fairly minimal 29.9% average vitamin C loss (table 2) [73, 75-77]. Steaming foods (in a microwave or stovetop) can be a good compromise to boiling. The vitamin C content is preserved fairly well in steaming, with only an average 14.3% loss (Table 2) [73, 75-77, 79].

Table 2: Vitamin C loss in vegetables with different cooking methods

Reference	Vegetable	Boiling	Stir Frying	Steaming
Hwang, Shin, Lee S, Lee J, & Yoo, 2012 [73]	Red Pepper	66.5% loss	14% loss	34.2% loss
Gil, Ferreres, & Tomás-Barberán, 1999 (boiling) [74]; Zeng, 2013 (steaming) [79]	Spinach	60% loss	(no data)	11.1% loss
Ahmed, & Ali, 2013 [75]	Cauliflower	50% loss	15% loss	15% loss
Xu et al., 2014 [76]	Red Cabbage	40% loss	62.5 % loss	6% loss
Yuan G, Sun, Yuan J, & Wang, 2009 [77]	Broccoli	38% loss	28% loss	5% loss
Average Loss:		50.9 %	29.9%	14.3 %

Food storage is also a major factor for maintaining adequate vitamin C levels, and it has been established that high temperature and/or long storage periods degrade the vitamin C concentration of foods [80-82]. If food will not be eaten immediately after purchasing, the best method of storage (to maintain the highest level of vitamin C) would be freezing. For example, baby corn loses 11.6% after 3 months (0°C) [83], and broccoli and peas lose 10% after 12 months (-20°C) [84].

For individuals who have access to fresh produce, the necessary amount needed to achieve the RDA of 75 mg (women) and 90 mg (men) [23] is not difficult to attain. As shown in table 3, some common foods (such as kiwi and red pepper) can provide more than double the RDA of vitamin C for men and women with just 1 cup. This is even more exaggerated in Rose hips, providing an incredible 473.3% RDA for men and 568% RDA for women (Table 3). If individuals abide by the recommendation to eat 5 servings of fruits and vegetables daily (or 400-500g as determined by the World Health Organization (WHO) and the Food and Agricultural Organization of the United Nations (FAO) [85]) then their vitamin C intake would be between 210-280 mg [53]. In summary, some of the best ways to ensure proper intake are: consume fruits, vegetables and juices high in vitamin C; choose fresh and/or frozen products over canned when available; consume fresh produce/juice within a week of purchasing; eat foods raw or cook by steaming; and store produce not intended for immediate use in freezer.

Table 3: Amount of vitamin C in fruits and vegetables

Food	Measurement		Vitamin C (mg)	% RDA	
	Serving	Weight (g)		Men	Women
Rose hips (raw)	½ cup	100	426	473.3%	568%
Gold kiwifruit (raw)	1 cup, sliced	186	196	217.8%	261.3%
Sweet red pepper (raw)	1 cup, chopped	149	190.4	211.6%	253.9%
Broccoli (boiled)	1 cup, chopped	156	101.2	112.4%	134.9%
Orange (raw)	1 cup, sections	180	95.8	106.4%	127.7%
Strawberries (raw)	1 cup, halves	152	89.4	99.3%	119.2%
Orange juice	1 cup	249	83.7	93%	111.6%
Grapefruit (raw)	1 cup, sections	230	79.1	87.9%	105.5%
Cherry tomatoes (raw)	1 cup	149	20.4	22.7%	27.2%
Spinach (boiled)	1 cup	180	17.6	19.6%	23.5%
Potato (baked)	1 potato w/ skin	148	14.2	15.8%	18.9%

(Modified from U.S. Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference Release 27 [86], & National Nutrient Database for Standard Reference [87])

Even with the high vitamin C content of some foods, many individuals are still not reaching an adequate intake. One way to facilitate an increase of vitamin C in the diet is to supplement foods with additional vitamin C. A review of the pros and cons of vitamin C enhancement in

plants has been completed, including methods using biosynthesis improvement and vitamin C recycling [2]. This type of genetic engineering could help communities with a limited variety of produce. For example, potatoes are a heavily consumed vegetable in both whole and processed varieties, and individuals usually have access to them in one form or another. Studies have shown 2-3 fold increases in typical vitamin C levels of potatoes using the overexpression of genes [88-89]. With that improvement, potatoes could compete with the vitamin C amounts in fresh produce not available to some communities, such as grapefruit and cherry tomatoes.

MANAGEMENT AND PREVENTION OF CHRONIC DISEASES WITH VITAMIN C:

Though proper vitamin C intake can improve our diets and health, there is also evidence to suggest successful clinical applications in disease prevention and management.

There are many studies which demonstrate the disease management benefits of vitamin C on certain diseases, with a few shown in table 4. One study has shown that vitamin C can help treat diseases that current medicines cannot, such as Epstein-Barr virus (EBV). After high dose (7.5-50 g) IV vitamin C treatments, subjects with EBV showed a 40% decrease in early antibody (EA) immunoglobulin G (IgG) levels and a positive effect on disease duration (table 4) [90]. In a review on the effect of vitamin C on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), human trials have shown that individuals afflicted with those diseases tend to have low vitamin C plasma concentrations and/or a low dietary intake of vitamin C [91]. This review also highlighted that treating those diseases with vitamin C (300-1000 mg daily) can facilitate improvement with disease symptoms (i.e. steatosis) [91]. One of those review studies by Kawanaka et.al., (2013) is highlighted in table 4 [92]. Another major health issue is hypertension, and vitamin C has been shown to lower blood pressure. After an initial vitamin C dose of 2 g, and subsequent daily doses of 500 mg for one month, the participants' mean blood pressure dropped 9.1%, providing evidence that long-term vitamin C treatment can reduce blood pressure in patients with hypertension (table 4) [93]. The use of vitamin C can also aid patients who are undergoing treatment. One study on breast cancer patients undergoing chemotherapy/radiotherapy showed that a once weekly IV dose of 7.5 g vitamin C decreased their overall side-effects (such as nausea, loss of appetite, and fatigue) by 37.5%, showcasing its benefits in conjunction with standard therapies (Table 4) [94]. Another study on the use of supplemental oxygen revealed that hyperoxia can cause negative side effects, including reduced coronary blood velocity (CBV) by 28%, increased relative coronary resistance by 34%, and decreased left ventricular (LV) systolic velocity by 11%, all of which were eliminated with an IV dose of 3 g vitamin C [95].

In addition to disease management, vitamin C is also a good indicator of certain diseases. Low plasma levels of vitamin C are associated with oxidative stress, a good marker for certain diseases. As mentioned earlier, vitamin C helps to reduce oxidative stress in the body, such as malonyldialdehyde (MDA), which leads to an inverse correlation. Patients with chronic obstructive pulmonary disease (COPD) can have a 55.3% higher level of MDA and a 69.4% lower level of vitamin C than healthy controls [96]. Patients with chronic hepatitis C virus (CHC) can have a 41.5% higher level of MDA and a 27.5% lower level of vitamin C than healthy controls [97]. Patients with chronic kidney disease (CKD) also show an inverse correlation between MDA and vitamin C, with a correlation coefficient of -0.36 [98]. Vitamin C

plasma levels have also an inverse correlation with the incidence of heart disease, with every 20 µmol/L increase in plasma yielding a 17% decrease in risk for heart failure [99].

Table 4: Disease management with vitamin C

Study/EBM*	Analysts	N	Patients	Duration	Intervention	Outcome
A clinical study of EBV infected patients at the Riordan Clinic treated with IV vitamin C between 1997-2006, compared to a systematic review of current vitamin C/viral infection evidence. (Mikirova & Hunninghake, 2014 [90])	IV vitamin C	218 total; 35 with full data	Patients with elevated levels of EBV EA IgG (range 25 to 211 AU)	Varying durations.	IV vitamin C ranging from 7.5 g-50 g, administered 1-20 times.	Average improvement of 40% in EBV EA IgG levels; a 2.7% improvement was seen with each additional IV vitamin C treatment. Positive effect on disease duration and reducing viral antibodies.
A nonrandomized pilot study evaluating the effects of antioxidant therapy on patients with liver disease. (Kawanaka et al., 2013 [92])	Oral vitamin C and E	23	Patients with nonalcoholic steatohepatitis (NASH)	12 months	300 mg/day of both vitamin C and E	Decrease of 58.2% serum alanine aminotransferase and 49.4% of high-sensitivity C-reactive protein Combination therapy of vitamins C and E minimize damage and slow disease progression.
A randomized, double-blind, placebo-controlled study evaluating the effects of ascorbic acid on blood pressure. (Duffy et al., 1999 [93])	Oral vitamin C	45 initial; 39 final	Patients with hypertension	1 month	One initial 2 g dose, then 500 mg/day for 30 days	Decrease in systolic blood pressure (8.4%) and mean blood pressure (9.1%) Long-term vitamin C treatment reduces blood pressure in patients with hypertension.
An epidemiological, retrospective cohort study with parallel groups evaluating the safety and efficacy of vitamin C for breast cancer patients. (Vollbracht et al., 2011 [94])	IV vitamin C- Injektopas®/ Pascorbin®	125	Patients with breast cancer in their first postoperative year	12 months	7.5 g once a week for 4 weeks during adjuvant therapies (not administered on the days of chemo- and radiotherapy).	37.5% reduction in complaints from side-effects during therapy and 52.5% reduction during aftercare compared to control IV vitamin C optimizes standard tumor-destructive therapies and reduces quality of life-related side-effects.

*Evidence-based medicine

There are many ways in which vitamin C can be used as a preventative measure, rather than a treatment. Though most research focuses on oral or IV routes, there is evidence to suggest the effectiveness of topical applications as well. A solution containing 10% l-ascorbic acid in a hydroglycolic base (water, butylene glycol, dipropylene glycol, and ethanol), 0.5% ferulic acid and 2% phloretin has been shown to decrease the incidence of sunburned cells by ~90.2%, and DNA damage (thymine dimers) by ~92.7% [100]. Topical vitamin C solutions can have protective effects against UV radiation, which can act as a potential prevention against certain skin cancers. Preventative effects have also been seen in diabetes, and individuals diagnosed with that disease are at risk for many complications. One of those complications involves high glucose concentrations, which activates the receptor for advanced glycation end products (RAGE) that can lead to pericyte apoptosis [101]. In a cell-culture study, ascorbate loading of 100 μM was shown to completely prevent apoptosis due to RAGE activation, presenting the importance for diabetes patients to ingest enough vitamin C to maintain plasma concentrations of 50–100 μM [101]. Outside of the lab, evaluations of vitamin C consumption and its preventative effects on certain populations have shown some promising results. Through the third National Health and Nutrition Examination Survey, women were shown to have a 13% lower prevalence of clinical gallbladder disease with each 27 $\mu\text{mol/L}$ increase in their serum ascorbic acid level [102]. In an 11 year cohort study on the association of vitamin supplementation and upper gastrointestinal cancers, it was shown that multivitamin use did not help to lower risk, but specific vitamin C supplementation revealed a 21% lower risk of gastric noncardia adenocarcinoma (GNCA) [103]. Higher plasma levels of vitamin C have also been linked with a decrease in overall mortality, the greatest preventative measure. In a prospective population study, it was found that “a 20 $\mu\text{mol/L}$ increase in plasma ascorbic acid was associated with about a 20% decline in death due to all cause, cardiovascular disease, and ischaemic heart disease” [104].

CONCLUSIONS:

Vitamin C is a powerful functional food ingredient with numerous health applications. Proper intake over a lifetime helps maintain our current health and prevents future ailments. At least 10 mg daily will prevent clinical deficiency and scurvy, although current research suggests 90-500 mg daily for optimal benefits. Much higher doses (many beyond the 2 g UL) are used in the clinical setting, with the greatest blood plasma levels achieved through IV injection. Proper doses for treatment are extremely variable, and depend upon the disease being treated. The risks of high-dose vitamin C supplementation are almost negligible when compared to some current treatments. That being said, extremely high-doses should be administered with caution and treated as a pharmaceutical agent. In regards to disease management, continued clinical and epidemiological research will help to further understand and confirm the positive health effects from vitamin C in the prevention and treatment of numerous conditions. In terms of the general public, studies on the long-term effects of over-the-counter oral supplementation should be focused on, due to increasing awareness of vitamin C benefits. Future studies should also focus on how to safely and effectively implement vitamin C into diets of populations at risk for deficiency.

List of Abbreviations: 2,2'-azinobis (3-ethylbenzothiazoline-6) sulfonic acid, ABTS; chloramphenicol acetyltransferase, CAT; chronic hepatitis C virus, CHC; chronic kidney disease, CKD; chronic obstructive pulmonary disease, COPD; coronary blood velocity, CBV; dehydroascorbic acid, DHA; early antibody, EA; Epstein-Barr virus, EBV; estimated average requirement, EAR; Food and Agricultural Organization of the United Nations, FAO; food and nutrition board, FNB; gastric noncardia adenocarcinoma, GNCA; glucose transporter, GLUT; gulonolactone oxidase, GLO; immunoglobulin G, IgG; institute of medicine, IOM; intravenous, IV; left ventricular, LV; low-density lipoprotein, LDL; maintenance haemodialysis, MHD; malondialdehyde, MDA; malonyldialdehyde, MDA; non-alcoholic fatty liver disease, NAFLD; non-alcoholic steatohepatitis, NASH; reactive oxygen species, ROS; receptor for advanced glycation end products, RAGE; recommended dietary allowances, RDA; sodium-dependent vitamin C transporter, SVCT; superoxide dismutase, SOD; thiobarbituric acid reactive species, TBARS; total antioxidant capacity, TAC; United States department of agriculture, USDA; upper tolerable limit, UL; World Health Organization, WHO;

Competing Interests: The authors have no financial interests or any other conflicts of interest to disclose.

Authors' Contributions: All authors contributed to this review.

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