International Journal of Science Academic Research
Vol. 01, Issue 08, pp.532-542, November, 2020
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

ASCORBIC ACID (VITAMIN C) AND ITS EFFECT ON 18 MINERALS BIOAVAILABILITY IN HUMAN NUTRITION

***Dana N. Abdelrahim, Hasan M. Al-Amery and Lujain M. Shawareb**

Department of Nutrition and Food Technology, Faculty of Agriculture, The University of Jordan, Amman – Jordan

Received 17th September 2020; **Accepted** 20th October 2020; **Published online** 16th November 2020

Abstract

This review aimed to assess the relationship between ascorbic acid and number of minerals in the human body. Although there is a lack of available data concerned about the interaction between ascorbic acid and minerals but by reviewing the available literature, we concluded that nutrients bioavailability varies from food item to another and it was notable that it affects the incidence of mineral deficiency. Assessing the effect of ascorbic acid on minerals bioavailability can overcome some nutritional problems related to mineral deficiency consequences. Ascorbic acid intake has a synergistic effect on iron calcium, zinc, magnesium, and cobalt absorption, while an antagonistic effect was seen in copper, nickel and manganese, cadmium and mercury. Both synergistic and antagonistic effects were seen in selenium upon the addition of ascorbic acid and no significant effect was seen on phosphorus. Finally, up to our knowledge there is no available data about the interaction between potassium, molybdenum, vanadium, silicon, sulfur and iodine with ascorbic acid. Therefore, it is important to review this topic and update it.

Keywords: Ascorbic Acid, Bioavailability, Interaction, Essential Minerals, Vitamin C.

INTRODUCTION

Micronutrients (vitamins and minerals) interaction can affect the nutritional status.[1]The biological effects of most micronutrients are repeatedly studied only in isolation. But nutrients do not act as independent units and are interconnected with other nutrients in terms of function and metabolism.[2] Thus, the actual level of any nutrients either in the diet or metabolically in human body can affect the required level of a particular nutrient.[2]Many pathological conditions may results from deficiency or excess of one or more nutrients in the diet.[3]The objective of this review is to overview the interactions between Ascorbic acid(vitamin C) and some of minerals that are important for the human body, and its effect on their bioavailability.

ASCORBIC ACID

Definition, Structure and Characterization

Ascorbic acid is a instantaneously well-known and remarkably poorly understood complex,[4] it is commonly called Vitamin C.[5]It is a water soluble vitamin, [6]it serves as the major aqueous phase reducing agent in the body.[7] The major dietary forms of vitamin C are the reduced (L-ascorbic acid) or the oxidized (dehydroascorbic acid) form,[8] the summation of these two forms is the total vitamin C.[9] The active form of vitamin C, L-ascorbic acid (AA) in tissues can be regenerated by the reduction of its oxidized forms, dehydroascorbic acid (DHAA) and the free radical (ascorbate) in a glutathione (GSH) mediated process.[10] Ascorbic acid is a chemically defined compound, its formula $C_6H_8O_6$is shown in figure 1, and its molecular weight is 176.13 g/mol,[11]it is ketolactone with two ionizable hydroxyl groups.[12]Sometimes it is considered as a weak sugar acid, due to its structural similarity with glucose.[8]The IUPAC name of Ascorbic acid is 2-oxo-L-threo-hexono-1, 4-lactone-2, 3-enediol.[8]

Corresponding Author:** ***Dana N. Abdelrahim,
Department of Nutrition and Food Technology, Faculty of Agriculture, The University of Jordan, Amman – Jordan

L-ascorbic acid has a white to very pale-yellow color, it is a crystalline powder with a pleasant sharp acidic taste and it is almost odorless.[13] Ascorbic acid (vitamin C) is highly sensitive to heat, light, moisture and oxygen conditions.[5]In the dry state, ascorbic acid is practically stable in air, but it rapidly oxidizes in solutions, also it is sensitive to interaction with copper, iron, and tin.[11]Cooking, storage and food processing typically accelerate the oxidation reaction rate which leads to destroy ascorbic acid. Stability of ascorbic acid can be enhanced by low pH acidic values while high pH alkaline values are deleterious.[11] So, when assessing ascorbic acid (vitamin C) intake, many factors should be taken into consideration. Vitamin C is only synthesized by eukaryotes.[4] Humans are unable to synthesize vitamin,[5] Therefore, Humans must completely rely on daily consumption from dietary sources to maintain adequate levels of the vitamin that cover their needs.[8] Citrus fruits like oranges and lemons are enriched in vitamin C.[8] Other fruits like watermelon, strawberries, pineapple, grapes, papaya, mango, tomatoes, cherries, raspberries, berries, green and red peppers, broccoli and green leafy vegetables like cabbage and cauliflower contain vitamin C in sufficient amounts,[6,8] and it is not detected in meat, cereals and dairy products.[5] About 80-90% of ascorbic acid is absorbed in the small intestine,[5]As intraluminal concentrations increases the percentage of absorbed vitamin C decreases.[6] Ascorbic Acid circulates freely in plasma with red blood cell and leukocytes and then enters the tissues to be utilized.[5]

Ascorbic acid Functions

Ascorbic acid (vitamin C) is exogenous effective antioxidant and it is one of the bioactive plant-derived compounds.[15]In the skin, ascorbic Acid is the most abundant antioxidant.[7]In respect to its antioxidant properties, it is considered to be more reactive than glutathione (GSH), it also could be seen as a preferred route due to GSH electron donation which produces the reactive and damaging thiol radical.[14] It has also anantimicrobial,[5]antiatherogenic, and immunomodulatory functions.[8] It is an essential co-factor for collagen, carnitine and neurotransmitterbiosynthesis.[6,8]

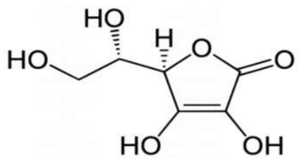

Figure 1. Structure of Ascorbic Acid (Sengupta *et al.,* 2020)

It also plays many important roles in the bone formation, wound healing, metabolic functions, maintenance of healthy gums, and acts as a cofactor for a lot of enzymatic reactions.[5] For productive and sustainable, consistent supply of nutritionally balanced food containing appropriate ratios of all essential micronutrients is a prerequisite.[3]Vitamin C deficiency usually occurs in cases of decreased intake or increased requirements or in case of losses.[6] Diverse groups of people are at high risk for inadequate intake of the vitamin, these may include the elderly, smokers, patients on parenteral nutrition and different illness cases.[6] Diet rich in vitamin C have significant effect on preventing cardiovascular diseases and some types of cancers.[5]Ascorbic acid has proven its activity in high doses for cancer therapy due to its antitumor effect.[8,16] It also accelerates fat metabolism, by controlling fatty plaques deposition on the walls of blood vessel.[5] In the presence of free iron and/or copper, high dosages of vitamin C has virucidal activity, apparently through generation of some radical species such as hydrogen peroxide or the contribution of low pH on antiviral effects of vitamin C.[17] The basis for using high doses of vitamin C to prevent and fight virus-caused illness may be sketched back to vitamin C's early success in contradiction of polio, which was first reported in the late 1940s.[18]Nowadays it is considered as a good protector from corona virus and other respiratory infections.[18] The addition of vitamin C to foods processing or packaging can protects aroma, color and nutrient content. In meat processing, ascorbic acid makes the reduction of the added amounts of residual nitrite content possible in the product. The addition of ascorbic acid to the fresh flour improves the flour baking characteristics.[11]Ascorbate can reduce amino acid radicals like tyrosine and tryptophan effectively.[19]Anthocyanins and phenolic acids were more unstable in the presence of ascorbic acid, while stability of flavonols was enhanced by its presence.[20] The daily dietary requirements of ascorbic acid (vitamin C) for adults (> 19 y) are 75 mg/day and 90 mg/day for normal healthy women and men, respectively.[8]Saul et al.[18]recommend taking 3,000 milligrams (or more) of vitamin C daily to prevent or minimize symptoms of future viral infections. Consequently, scurvy is caused by vitamin C deficiency, which is presented by hemorrhage, hyperkeratosis, and hematological abnormalities.[6] Also, ascorbic acid deficiency can cause anemia, muscle degeneration, poor wound healing, capillary hemorrhaging, lassitude, vision problems, amendment of the extracellular matrix in blood vessels, skin, gums and tendons, bones and bone fragility and neurological disorders,[21]it also can weaken the immune system.[5]

BIOAVAILABILITY

The bioavailability is an important factor,[22] which can be defined as a key to the effectiveness of functional foods. Among functional food components, minerals have an essential role in a healthy life.[23] The bioavailability is considered as a measure of the rate and extent to which a matter reaches its site of action.[24] The bioavailability of a nutrient can be subdivided in three integral phases: (1) availability for absorption in the intestinal lumen; (2) absorption and/or retention in the body; (3) body utilization.[23] The total amount of a mineral in a food does not indicate the amount that is available to the body beyond absorption. Only a certain amount is bioavailable. Bioavailability or biological availability are terms used to describe the proportion of a nutrient in food that can be utilized for normal body functions. The term bioavailability was also introduced to better differentiate between the chemical availability and the availability in the bioassays.[23]

MINERALS

Minerals Bioavailability

Minerals are inorganic micronutrient that are required in small quantities,[3]but participate in orchestration of different biological processes that drive normal growth, development, and function.[25] Minerals are also essentially involved in the maintenance of the acid base balance, membrane potential generator (Na/K pump) and formation of bones and teeth;[3]and it is important as essential constituents of body fluids and tissues (osmoregulation); as components of enzyme systems and for normal nerve function.[25] Compared to data obtained on macronutrients needs, information on micronutrients needs and bioavailability specially minerals are scarce.[3]It was recently realized that the biological availability of minerals plays an important role in nutrition.[26] Food processing can have a positive impact through minerals enrichment, destruction of inhibitors or the formation of beneficial complex between food components and metal ions, thus enhancing their availability.[23] Calcium, cobalt, copper, iron, magnesium, manganese, molybdenum, phosphorus, selenium, iodine, potassium, sulfur, sodium and zinc are essential to mammalian nutrition, nickel, silicon and vanadium considered nonessential nutrients,[26] while Cadmium, lead, mercury, and aluminum are toxic metals that may interact metabolically to inhibit the absorption of nutritionally essential metals.[27] Deficiencies in essential mineral elements are seen as a major nutritional problem in the world these days.[23] Minerals play dynamic roles in body regulatory roles like wellbeing and disease prevention,[5] synthesis of tissues and organs.[26] Current methods to determine the bioavailability of metal ions in compositions rely on measuring the number of soluble ions in the compositions, and thus “bioavailable” metal ions. However, measuring solubility of metal ions alone may not provide accurate indication of bioavailability.[28] The main reported cause of minerals deficiency in the world’s population is low consumption.[5] The minerals bioavailability is influenced by many factors which may enhance or inhibit their absorption from the human diet. Commonly, organic acids act as absorption enhancers while polyphenols and dietary fibers are the inhibitors.[5]

Ascorbic acid / Minerals interactions

The main focus of attention of many studies is on ascorbic acid effect on mineral bioavailability,[2] but it still observed by few researches.[5]It is a very important area of research, it should be taken into consideration when initiating food supplementation and fortification programs to enhance or promote the absorption of some nutrients and protect humans from the adverse effect of inhibitors.[1]The main interaction of ascorbic acid with minerals happens in the gastrointestinal tract.

Table 1. Summary of Ascorbic Acid interactions with minerals in Human Body*

Mineral	Antagonistic Relationship	Synergistic Relationship	No Relationship	No available Data
Iron (Fe)		✓		
Calcium (Ca)		✓		
Copper (Cu)	✓			
Zinc (Zn)		✓		
Magnesium (Mg)		✓		
Cobalt (Co)		✓		
Nickel (Ni)	✓			
Selenium (Se)**	✓	✓		
Phosphorus (P)			✓	
Manganese (Mn)	✓			
Potassium (K)				✓
Molybdenum (Mo)				✓
Vanadium (V)				✓
Silicon (Si)				✓
Sulfur (S)				✓
Iodine (I)				✓
Mercury (Hg)	✓			
Cadmium (Cd)	✓			

* The data summarized in this table was depended on last updated research data for each mineral)
**Selenium has both synergistic and antagonistic interaction with ascorbic acid based on the ingested compound

The net effect of these promotors and inhibitors on mineral absorption from typical diets naturally consumed is not widely investigated. Knudsen, et al.[29] suggested that low molecular weight organic acids such as amino acids and ascorbic acid maybe promote absorption of trace elements by increasing their solubility. Ascorbic acid has a considerable effects on inhibiting or enhancing the uptake of minerals into the mucosal cells by influencing some of the transport proteins in intracellular binding systems for minerals in intestine.[26] In general, Ascorbic acid is a good enhancer of some mineral bioavailability.[26] Luckily, it has not increased the bioavailability of some toxic minerals. In this review, we studied the effect of Ascorbic acid on 18 minerals bioavailability which are: Iron (Fe), Calcium (Ca), Copper (Cu), Zinc (Zn), Magnesium (Mg), Nickel (Ni), Selenium (Se), Phosphorus (P), Manganese (Mn), Potassium (K), Molybdenum (Mn), Vanadium (V),Silicon (Si), Sulfur (S), Iodine (I), Mercury (Hg) and Cadmium (Cd).

Ascorbic acid and Iron (Fe): Iron has vital roles in biochemistry and metabolism of cells which include binding capacity of oxygen to heme protein in the blood and the formation of active sites in enzymes which are elaborated in the mitochondrial electron transport chain.[3]Ascorbic acid is also have a role in DNA (Deoxyribonucleic acid) synthesis, energy production and metabolism.[5]The recommended daily allowance from iron for adults ranges from 17 to 21 mg/day,[30] Approximately half of the iron in meat, fish, and poultry is heme iron. About 15% to 35% of heme iron is absorbed depending on an individual's iron stores. Food contains more nonheme iron makes the larger contribution to the body's iron pool even with its lower absorption rate (2% to 20%).[31] Iron deficiency is known to influence oxidative stress in mammals.[3] Iron from food is absorbed by the intestinal mucosa from two separated pools of heme and nonheme iron.[11]Heme iron is less affected by meal composition and well absorbed,[32] thus ascorbic acid has no effect on heme iron absorption.[5] The possibility of existence of an important interaction of ascorbic acid and iron in the human intestine was first suggested in 1940.[26] Ascorbic acid stated as the most efficient promoter or enhancer of iron absorption.[33] Nonheme iron is greatly influenced by meal composition, and its absorption is enhanced by ascorbic acid.[5] Non-heme iron absorption can be improved by carotenes, retinoids, citric, tartaric and malic acids.[34] Ascorbic acid is a strong reducing agent, its ability to donate electrons permits it to act as a free radical scavenger,[4] it increases iron absorption[35] by allowing its effective transport through microvilli of the duodenum[34] by reduction mechanisms involving ferric (Fe^{3+}) to ferrous (Fe^{2+}) conversions,[15,34] which is more bio available and less dominant in foods,[11] ascorbic acid also elevates the level of absorption of iron within the cell from dietary iron sources.[8] The rate of reduction decreases as the pH increases and the effective reducing effect of ascorbic acid disappears above 6.0 pH.[11] Vitamin C also regulates iron homeostasis by inhibiting hepcidin expression, potentially helping attenuate iron deficiency.[15]It can also regulate iron metabolism; it is ideal candidates to help managing oxidative stress, particularly in the case of iron overload and/or iron deficiency.[15] The effect of ascorbic acid is so powerful that it can reverse the effect of inhibiting substances such as coffee and tea tannins.[1,34] Phytates and polyphenols in plant foods usually binds with non-heme iron and thus inhibit its absorption.[36] Therefore, several hundred milligrams of ascorbic acids are needed to reverse the inhibitory effect of phytate and polyphenols.[11,37] Also, ascorbic acid can counteract the inhibiting effect of such minerals as calcium/phosphate.[32] To promote absorption in the presence of inhibitors in high amounts, ascorbic acid needs to be added at a molar ratio in excess of 4:1, which may be enhance the absorption.[11]The addition of ascorbic acid to the beverages fortified with $FeSO_4$ in a molar ratio of 2:1 was shown to overcome the inhibitory effect on iron absorption by calcium.[35]The sharp increase in iron absorption with the addition of ascorbic acid decreases at high ratios and ascorbic acid has an optimal level which upon the additional nutritional benefit is negligible.[11] An enhancing effect of ascorbic acid is well proven for non-heme iron absorption.[29]consumption of iron-rich foods along with ascorbic acid (vitamin C) is recommended for improving iron bioavailability and promote iron absorption to prevent anemia.[34,11]

Ascorbic acid and Calcium (Ca): Calcium (Ca) is an important mineral for bone and teeth health. Due to its vital role in human health, people are concerned about calcium intake through diet and from other supplements. The actual absorbed amount by the body plays important role and should be taken care of as the ingested amount.[38] Calcium is one of the most essential mineral for normal growth, it plays a vital role in healthy bone mineralization,[38]blood clotting, muscle contraction, enzyme regulation, nerve conduction, weight loss and many others.[5] In childhood and adulthood, low calcium intake has been connected with enlarged risk of osteoporosis, fluorosis and bone fractures.[38]Calcium's recommended dietary allowance (RDA)differs between 800-1300 mg/d for adolescents and 1000 mg/d for adults rising to 1200 mg/d for the elderly.[38] It was estimated that the respective estimated bioavailability of calcium is 30%.[39] Past decade researches stated that no significant effect of ascorbic acid supplementation on calcium's bioavailability as reported by two reserarches.[40,41] One year after; Mehansho, et al.[42] reported that the addition of ascorbic acid increase 33 to 42.8% of calcium absorption. Although ascorbic acid has a little or no effect on calcium bioavailability, it increased calcium solubility by decreasing the solution's pH. By the development of research tools, nowadays it was confirmed that calcium bioavailability or absorption rate was significantly enhanced by ascorbic acid and this enhancement is independent of its pH and ascorbic acid content.[43,44] Recently it was found that the addition of ascorbic acid in selected food samples showed an increase in calcium absorption.[5]

Ascorbic acid and Copper (Cu): Copper (Cu) is a micronutrient obtained from the diet and plays a critical role in human growth, development and maintenance.[45] The human gastrointestinal tract can absorb 30% to 40% of ingested copper from the consumption of typical diets.[46] It is a bivalent metal ion that can be exist in both the cuprous (Cu^{+1}) and cupric (Cu^{2+}) states. Its capacity to readily gain and donate electrons makes it important in various metabolic pathways.[45] Copper is act as a cofactor for enzymes involved in the mitochondrial electron transport chain, reactive oxygen species detoxification, iron transport, connective tissue metabolism, melanin pigment production, synthesis of amidated neuropeptides, and catecholamine metabolism.[45] Growth retardation, mortality, reduction in the hepatic and blood copper concentration and toxic anemia is the result of copper absorption and accumulation in the body, all of these symptoms can be eliminated by inhibition of intestinal copper absorption which caused by ascorbic acid addition.[26] As also confirmed by a more recent study done by Singh and Prasad[5]that ascorbic acid inhibits the dietary absorption of copper. Ascorbic acid is the most significant organic acid known to have a negative effect on copper absorption,[46]this effect is attributed to the reduction of cuprous ions to cupric ions, the latter being less well.[47] It has, however, been suggested that long-term ascorbic acid (vitamin C) supplementation may depress the absorption of copper.[1,48] It was reported that ascorbic acid reduced the concentration of soluble copper in the small intestine of the rat and inhibits biliary copper excretion.[44] After longer feeding periods, the ascorbic acid-induced depression of copper absorption may not be observed because the reduced copper status raises the efficiency of copperabsorption.[49]

Ascorbic acid and Zinc (Zn): Zinc (Zn) is an essential trace mineral mandatory for the human body due to its significant role in cell growth and replication, bone formation, skin integrity, immune system function and sexual maturation.[5]zinc bioavailability is an important factor that has been taken into consideration in biofortification programs.[33]It was estimated that the respective estimated bioavailability of zinc is 30%.[39] Zinc has earned appreciation recently as a micronutrient of outstanding and diverse biological, clinical, and global public health importance.[50]The principal of absorption regulation in the enterocyte by zinc transporters, together with saturation kinetics of the absorption process into and across the enterocyte means whole-body zinc homeostasis is maintained.[50] No biomarkers of zinc uptake,[33] while Metallothionein (a cytoplasmic protein that stores zinc) has been used as an indicator of zinc uptake. But it’s not specific for zinc, this protein may also bind and store other metals, such as copper, selenium, cadmium, mercury, silver, and arsenic, this makes its application as a biomarker for zinc bioavailability questionable.[33] One of the simplest methods assess fecal and urinary excretion levels and then differentially calculate the indirectly absorption/retention of ingested zinc.[33] Different factors may affect the zinc bioavailability, Such as phytic acid and ascorbic acid. The availability of zinc is strong negatively affected by the presence of phytic acid.[29]Phytate is the only considerable dietary factor that inhibits zinc absorption.[50] Cooking process seems does not affect Zinc bioavailability.[51] Zinc is one of the most commonly targeted micronutrients which has high prevalence of deficiencies in children and women of childbearing age.[33] Old researches failed to improve the impact of ascorbic acid on the absorption of zinc in humans and the serum zinc level at any dose.[26,52,53] Which was still confirmed few years after by Sandstrom,[1] who stated that zinc absorption seemed to be unaffected by ascorbic acid addition. Etcheverry et al.[54] suggests also that ascorbic acid not plays a role in zinc bioavailability. The supplementation of ascorbic acid decreased zinc utilization and a significantly increased fecal zinc loss of vegetarian subjects as suggested by Kies et al.[52] Recently, it was found that organic acids, such as malic, citric, lactic and ascorbic acid are likely to improve zinc absorption.[51] So, researcher condensate their efforts on this area of research to conclude that, the ascorbic acid could relatively enhance the bioavailability of zinc from other components of the diet.[5,9]

Ascorbic acid and Magnesium (Mg): Magnesium (Mg^{+2}) is an important electrolyte and plays a central role in several cellular functions,[55] in this manner, it plays an important role in the physiological function of the brain, heart, and skeletal muscle. Magnesium is the second most abundant intracellular cation and the fourth most predominant cation in the body.[56] Magnesium is an essential cofactor for the activation of 80% of all cellular enzymes regulating diverse biochemical reactions[25], including energy metabolism, protein synthesis, muscle and nerve functions, blood pressure and blood glucosecontrol,[57] and is an important contributor to bone health.[25] The human body normally contains 1750 to 2400 mEq of magnesium.[58]About 67% of the body Mg is concentrated in bone and it makes up about 1% of the total bone mineral content,[25] also in muscles (20%) and non-muscle soft tissues (11%),[58] and only 1.3% of the total magnesium pool is extracellular.[56] Magnesium is not synthesized in the body and should be provided by external intake.[59] Normally about 7.4 mEq (90 mg) of dietary magnesium is eaten per meal. However, when a magnesium supplement is prescribed for suspected or overt magnesium deficiency, 20 mEq of elemental Mg may be ingested in a single dose.[58] Roughly, 30% of ingested magnesium with food or drinking water is absorbed in the intestine.[59] The concentration of absorbed magnesium ions in the small intestine depends on the status of body magnesium (increased in case of Mg^{2+} deficiency) [56,57]. Oral ingestion of increasingly high doses of magnesium does not lead to proportionally increased intestinal absorption.[59] Magnesium homeostasis is further regulated through the secretion and reabsorption in the kidneys, where about 95% of the filtered magnesium is reabsorbed.[57] Modern western diet and lifestyle lead to low magnesium intake and circulating levels, often associated with a range of metabolic changes and pathologies, So, it is recommended to increase magnesium intake by adequate diet or by supplements for some medical conditions because some drugs can deplete Mg levels.[59] The Recommended Daily Allowance for dietary magnesium (RDA) of 320 to 420 mg/day,[57] while the average daily intake of magnesium is 250 to 370 mg.[56] Upper tolerable intake Level of magnesium is 250 mg magnesium/person/day.[60] Magnesium is abundant in foods, but its content varies considerably. Leafy vegetables, grains and nuts, generally have higher magnesium content.[60]Protein, Fiber and phosphorus be found to affect magnesium bioavailability obtained from foods.[61] It was estimated that the respective estimated bioavailability of magnesium is 50%.[39] The bio accessibility of magnesium was high, indicating that the food matrix had no or little effect.[62]Measuring magnesium bioavailability is complicated because magnesium serum concentrations are extraordinarily well-regulated, the magnesium absorption could be measured from measuring the magnesium renal excretion.[55] Supplementation of magnesium could be as organic acid compound like (ascorbate, citrate, aspartate, lactate and gluconate) or inorganic compound like(oxide, chloride, sulfate and carbonate).[59] Magnesium bioavailability could be improved by novel formulations based on soluble salts.[59] Kappeler, et al.[55] confirmed that Mg organic compounds may be more suitable to optimize dietary magnesium intake in comparison to the supplementation with inorganic compounds. Magnesium ions from magnesium ascorbate were absorbed after the first 15 minutes to the highest extent of all salts.[60] The solubility of magnesium ascorbate is more than 95 g/100 mL.[60] It was suggested that Mg ion supplementation is an attractive cofactor that could increase the anticancer effects of vitamin C therapy.[16] Magnesium Ascorbate are described as antioxidant and skin conditioning agents.[44] The Panel concludes that the bioavailability of magnesium and vitamin C from the sources of magnesium ascorbate is not expected to differ from that of already permitted sources of magnesium and vitamin C for food supplements.[60] To the best of our knowledge, not much research has been conducted on magnesium bioavailability and no recent researches studied the effect of ascorbic acid on magnesium bioavailability.

Ascorbic acid and Cobalt (Co): Cobalt (Co) occurs naturally as a mineral and is present in more than 100 natural or man-made compounds. Cobalt ion is an essential nutrient in several species, and consequently, cobalt salts are used as nutritive supplements in feedstock and pharmaceutical industries.[63] Many metal ions such as cobalt are known to have antimicrobial activity.[28] Their mode of action remains unclear but may involve oxidative stress, protein dysfunction of membrane damage in the target cells.[28] At trace levels, cobalt is present ubiquitously. Diet, like fish, green leafy vegetables, and cereals is the main source of cobalt for humans; intakes range from 3 to 82 mg Co/day in different countries of the world.[63]Cobalt is involved in mammalian metabolism by sensing oxygen deficiency in animal cells by modulating transcriptional activator hypoxia-inducible factor, stimulating erythropoietin production and increasing erythropoiesis.[63] Cobalt forms the core of vitamin B_{12}, an essential nutrient for humans. In this form, it is required for the production of red blood cell (RBC), the prevention of pernicious anemia, in the formation of DNA, the synthesis of fatty acids and in energy metabolism. Cobalt ion absorption occurs in the duodenum and proximal jejunum and is facilitated by Divalent Metal Transporter 1, a protein also responsible for the absorption of other divalent metal.[63] A series of studies conducted on human volunteers in the Division of Human Nutrition and Biology at the Institute of Nutrition of Central America and Panama, didn't show any statistical significant difference in regard to ascorbic acid effecting the absorption of radiocobalt in aqueous solution when they employed the radiocobalt absorption test.[26]Valberg et al.[64] stated that the ascorbic acid addition did not have appreciable effect on cobalt's fecal excretion. Which indicates that ascorbic acid has no effect of cobalt absorption in humans, which was confirmed by Solomons et al.[65] who stated that ascorbic acid has no effect on inorganic cobalt absorption. On the other hand, Afolaranmi et al.[66] saw an increase in fecal excretion in rats when ascorbic acid was added to cobalt so he suggested that ascorbic acid may cause an increase in the elimination rate of cobalt. Yildirim et al.[67] stated that combining ascorbic acid to cobalt seemed to act in a synergistic state in regard to glucose homeostasis and he stated that ascorbic acid supplementation strengthens the cobalt action effectiveness. To the best of our knowledge, not much research has been conducted on cobalt bioavailability and no recent researches studied the effect of ascorbic acid on cobalt bioavailability.

Ascorbic acid and Nickel (Ni): Nickel (Ni) is a known to be hematotoxic, hepatotoxic, immunotoxic, pulmotoxic and nephrotoxic agent.[68]Nickel sulfate appears to be a potential hepatotoxic heavy metal that unfavorably affects the expression of genetic material by reducing DNA, RNA, and protein concentrations in the liver of albino rats.[69]The addition of ascorbic acid caused a significant depression in the rise of the plasma nickel compared to elemental nickel which indicates that ascorbic acid decreases Ni absorption.[26]It is concluded that vitamin C pretreatment effectively improved renal function and tissue damage caused by nickel.[70] The cellular ascorbate is greatly depleted by exposure to nickel (II) compounds. Thus, the depletion of ascorbate by chronic exposure to nickel could be deleterious for lung cells and may lead to lung cancer.[71] Reduction in ascorbate supplementation increased acute toxicity of nickel compounds in mice.[72] Ascorbic acid antagonizes metal toxicity such as nickel and silver by supplying electrons which protect the oxidation of -SH groups. This may also relate to reduced glutathione and sulfur-containing amino acids, Thus, protection from toxiciy.[73] Simultaneous treatment with ascorbic acid prevents the nickel stimulated alteration of nucleic acids concentration in the liver.[69] Treatment of L-ascorbic acid revealed a possible protective function on the toxic effect of nickel sulfate on testicular lipid peroxide and GSH concentration as well as antioxidant in enzymatic defense system.[74] Reports suggested the ability of ascorbic acid as a regulatory factor to influence gene expression, programmed cell death (Apoptosis) and other cellular functions of living system exposed to heavy metals including nickel.[75] To the best of our knowledge, not much researches has been conducted on nickel bioavailability and no recent researchers studied the effect of ascorbic acid on nickel bioavailability.

Ascorbic acid and Selenium (Se): Selenium (Se) functions as an important antioxidant within the body. Selenium is an essential mineral that functions in oxidant defense as a component of selenoproteins.[10] The importance of keeping adequate levels of selenium as well as vitamin C and vitamin E is underscored by studies indicating that low antioxidant status may be associated with increased risk of developing various diseases.[10] Given that Selenium, vitamin C (ascorbic acid) and vitamin E (alpha tocopherol) activities are interrelated, it is important to understand how deficiency in one or two of these antioxidants influences the other(s).[10] The combined effect of Selenium and ascorbic acid provides defense against alcohol-induced oxidative stress as demonstrated from the decreased levels of lipid peroxidation products and enhanced activities of scavenging enzyme.[76] Ascorbic acid acts as a reducing agent *in vitro*; it reduces selenate to selenite and selenide. Selenide is the most used form of the mineral in the body; reducing agents in the body tend to maintain selenium in its selenide form which may indicate that ascorbic acid increases Se bioavailability by keeping it in the selenide form.[26]Ascorbic acid (vitamin C) appears to affect Se availability both positively and negatively depending on chemical form and dietary conditions.[1] The *invitro* reaction between ascorbic acid and selenite can cause significant nutritional outcomes, it reduces selenium's bioavailability by precipitating the insoluble forms of selenium which are selenide.[77] The fractional absorption and the balance of Se were significantly greater when ascorbic acid supplementation was given.[77]It is clear that the utilization of this essential trace element can indeed be affected by ascorbic acid status.[78]It was seen that taking selenite and one gram of ascorbic acid together before a meal reduced selenium's availability to almost zero.[79] Dietary restriction of selenium and ascorbic acid decreased both the reduced and oxidized forms of vitamin C in tissues.[10] Given these findings and the data from recent studies indicate that selenium intake is inadequate in certain population groups. further studies evaluating the health implications and biological significance of reduced vitamin C and E status attributed to a low selenium or ascorbic acid diet are warranted.[10] The supplementation of ascorbic acid might have beneficial effect on the natural selenium's bioavailability but the availability of sodium selenate did not seem to be affected by ascorbic acid addition thus selenium's bioavailability in regard to ascorbic acid addition may vary according to the ingested selenium compound.[80]Ascorbic acid may have protective effects against organ di-selenide intoxication, since it decreases the deposition of selenium in organs such as liver and brain and reverses the decrease in the hemoglobin levels of animals.[81]Ascorbic acid (125 µmol/L) increased cellular selenium retention. The antitumorigenic effects of selenite and selenate can be enhanced by supplemental ascorbic acid or a related reducing compound.[82] It was concluded that for selenium "all usual dietary forms are absorbed quite efficiently." The 2000 report of the US Food and Nutrition Board advocated that most dietary Se is highly bioavailable. Most forms of selenium are efficiently absorbed, about 90% of seleno-methionine is absorbed; selenocysteine appears to be absorbed very well; 100% of selenate is absorbed, but a significant fraction is lost in the urine; and 50% of selenite is absorbed (depending on luminal interactions) and is better retained than selenate.[83]

Ascorbic acid and phosphorus (P): Phosphorus (P) is a universal mineral in nature and the second most plentiful mineral in the human body, phosphorus embodies around 1% of total body weight. With both an extracellular and intracellular spreading, phosphorus functions as a structural component of bones and teeth and DNA/RNA and enables the bipolarity of lipid membranes and circulating lipoproteins.[84] Metabolically, phosphorus functions in critical pathways to produce and store energy in phosphate bonds (ATP), buffer blood, regulate gene transcription, activate enzyme catalysis, and enable signal transduction of regulatory pathways affecting a variety of organ functions ranging from renal excretion to immune response.[84] Less than 1% of unbound inorganic phosphate (PO^{4-}) in the extracellular space is metabolically active and is now considered tightly maintained within a narrow serum concentration range (2.5–4.5 mg/dL) in adults.[84] Maintenance of phosphorus homeostasis in adults involves keeping urinary losses equivalent to net phosphorus absorption and equal amounts deposited and resorbed from bone. Complex organ network system (bone-kidney-intestine) is involved in the homeostatic control of serum phosphate homeostasis. [84] The total content of phosphorus in foods, as well as the chemical nature and physiologic characteristics of absorption will influence the hormonal regulation of phosphorus balance. There are two basic types of phosphorus in the food supply, natural and added, often referred to as organic and inorganic, which have very different rates and efficiencies of absorption.[84] Natural or organic phosphorus is slowly and less efficiently (40–60%) absorbed, whereas inorganic phosphorus salts added to food in processing are rapidly and efficiently (80–100%) absorbed.[84] Phosphorus deficiency or hypophosphatemia is rare in the healthy population, which is probably due to the widespread availability of phosphorus in most foods, milk and dairy being the greatest contributors followed by meat and poultry.[84] Serum inorganic phosphate was proposed as a biomarker to assess phosphorus nutritional adequacy by the Institute of Medicine to establish the dietary intake guidelines for phosphorus in 1997.[84] The recommended daily allowance of phosphorus for adults is 700 mg /day. A systematic review and meta-analysis done by Ke, et al.[85]confirmed that ascorbic acid could not influence the serum phosphorus in general, and it was implied that intravenous (IV) injection of ascorbic acid effectively reduced the serum phosphorus levels in HD patients.[85] To the best of our knowledge, not much research has been conducted on phosphorus bioavailability and no recent researchers studied the effect of ascorbic acid on phosphorus bioavailability.

Ascorbic acid and manganese (Mn): Manganese (Mn) is an essential micronutrient for intracellular events; it functions as a cofactor for a variety of enzymes, including arginase, Glutamine Synthetase (GS), pyruvate carboxylase and manganese superoxide dismutase (Mn-SOD).Manganese plays critical roles in development, reproduction, digestion, energy production, antioxidant defense, immune response and regulation of neuronal activities.[86] Manganese is a trace element of special interest because the possibilities of both deficiency and toxicity are exist, especially in infant nutrition.[87] The normal manganese concentrations in human blood ranges from 4 to 15 mg/L, and females tend to have 30% higher Mn level than males, probably due to a lower absorption rate in men. An average of 2.3 to 8.8 mg manganese is absorbed daily. Only 2.3 mg/day required for men and 1.8 mg/day for women. However, the daily absorption amount usually exceeds the actual need, thus extra manganese has to be eliminated.[86] Currently, dietary consumption is the main manganese exposure way. Manganese absorption via ingestion consider as the highest manganese amount and is also the safest way. About 3% to 5% of ingested manganese is absorbed in blood stream via the gastrointestinal tract through passive diffusion or active transport, regulated by manganese transporters and manganese binding proteins.[86] Infants and children tend to absorb higher quantity of manganese from diet due to their larger demands compared with adults.[86] Manganese carriers are not necessarily manganese - specific transporters, as they also regulate influx of other metals, such as iron (Fe), copper (Cu), zinc (Zn), calcium (Ca), etc. Therefore, metals presence in the biological media (blood, extracellular fluid, etc.) compete with manganese absorption.[86] Previous studies expected a reduction in intestinal manganese uptake in the presence of solution of dietary ascorbate,[26,44] because of its oxidation- reduction potential or its chelating ability, but this effect was minimal.[48] Currently, the mechanism behind manganese absorption in the intestine and delivery to the plasma remains unclear.[86] In addition, excretion is believed to be the major regulator of homeostatic control rather than absorption.[88] Several factors influence the absorption of manganese. Absorption of manganese inhibited by calcium addition, and not affected by the existence of iron and magnesium to wheat bread as well as phytate, phosphate and ascorbic acid to infant formula.[86]Ascorbicacid supplementation has been reported to significantly enhance the apparent retention of manganese at low manganeseintakes,[87]whereas increasing the ascorbic acid content of a phytic acid-containing soy formula had no effect on manganese absorption in adults.[88]To the best of our knowledge, not much research has been conducted on manganese bioavailability and no recent researchers studied the effect of ascorbic acid on manganese bioavailability.

Ascorbic acid and potassium (K): Potassium (K) has a major role in maintaining cellular function in excitable tissues (e.g., nerve and muscle), where it maintains the negative voltage across cell membranes. The ratio of the potassium concentration in the cell and out of the cell is a major factor of the resting membrane potential using Na^+-K^+-ATPase.[56] The total corporal potassium (K^+) stores are approximately 3000 to 4000 mEq (50 mEq/kg), and potassium is essentially an intracellular cation, with 95% to 98% found intracellularly. In humans, maintaining extracellular potassium in a narrow range is crucial for survival.[56] The normal potassium intake in the diet usually varies between 100 and 500 mmol/day.[56] Hence, potassium absorption percent is too high (reach 90%) in human body,[89] and its bioavailability estimated as 90%,[39] and its absorption by the gastrointestinal tract is fast, requiring a close control of the extracellular concentration,[56] So, we suggest that potassium does not need enhancers. To the best of our knowledge, not much research has been conducted on potassium bioavailability and no recent researchers studied the effect of ascorbic acid on potassium bioavailability.

Ascorbic acid and Molybdenum (Mo): Molybdenum (Mo) is trace element essential for almost all organisms it functions as an enzymatic cofactor by forming the catalytic site of a large variety of enzymes such as nitrogenase, nitrate reductases, sulphite oxidase and xanthine oxidoreductases.[90]Overall of 59% to 94% of dietary molybdenum is absorbed in gastrointestinal system depending on the ingested dose. Molybdenum deficiency is rare and is corelated with weakened reproductive functions and growth retardation. High amounts of molybdenum are toxic.[91]To the best of our knowledge, not much research has been conducted on molybdenum, bioavailability and no recent researchers studied the effect of ascorbic acid on molybdenum bioavailability.

Ascorbic Acid and Vanadium (V): Vanadium (V) is mainly found in bones, kidney and liver. Two main paths for the vanadium absorption, they are breathing and ingestion.[91] Vanadium is also found in potable water and its intake by this source depends on the daily ingested volume.[91] Vanadium, in the form of vanadium oxides, VO_4 or VO_5, is present in air in particulate form or absorbed to tiny dust particles and aerosols, and thus enters the lungs and the pulmonary system, from where it becomes circulated in the body after solubilization.[92]Vanadium deficiency in human is very rare.[91] The average body load of a human individual amounts is around one miligram.[92]Industrial exposure to high levels of airborne vanadium is the only way to develop the toxic effect. It is doubtful to exposes to this toxic effects as a result of the intake of large amounts of vanadium from the diet.[91]The low absorption rate of dietary vanadium and the rather efficient desorption of excess vanadium that has entered the blood and body tissues diminish toxic effects that can emerge.[92]To the best of our knowledge, not much research has been conducted on vanadium, bioavailability and no recent researchers studied the effect of ascorbic acid on vanadium bioavailability.

Ascorbic acid and Silicon (Si): Silicon (Si) is a beneficial trace element that is widely distributed in foods with several dietary sources of grains, root vegetables, bean, corn, fruits, dried fruits, nuts, and also drinking water. Silicon levels are higher in foods derived from plants.[91]It was demonstrated that silicon has an important role for in bone mineralization and connective tissue development. Also, silicon seemed to be involved in the formation of extracellular matrix components and in calcium metabolism. Silicon is claimed to have beneficial effects on several human disorders, for example, osteoporosis, aging of skin, hair, and nails and arteriosclerosis. But until today, no one has been able to confirm that silicon is an essential element for humann.[93] The amount of silicon in tissues decreases with age. Silicon improves the structure of hair, mails, skin and bone calcification. Regulates the immune system and inflammatory response. Accelerates the rate of bone mineralization. Mitigates the risk of atherosclerosis. Silicon protects against the toxic actions of aluminum. The amount of silicon in tissues decreases with age.[91] Hence, about 70%–80% of plasma silicon is eliminated by kidneys within 3–8 h after meal ingestion. Although there are several possible dietary sources, silicon bioavailability from foods is low. Thus, it may be sensible to increase intake through other advanced means such as biofortification of edible parts of plants.[91]To the best of our knowledge, not much research has been conducted on silicon, bioavailability and no recent researchers studied the effect of ascorbic acid on silicon bioavailability.

Ascorbic acid and Sulfur (S): Sulfur (S) is a vital essential element for humans, animals, and plants, which is a major component in the structure of many amino acids and enzymes. It is part of the amino acid methionine, which is an absolute dietary requirement. The amino acid cysteine also contains sulfur. In foods, sulfur can be found in their structure or can be added as preservative.[94] Many food items have high sulfur contents such as eggs, nuts, garlic, onions, vegetables, seafood, meat, and milk products.[94] To the best of our knowledge, not much research has been conducted on sulfur, bioavailability and no recent researches studied the effect of ascorbic acid on sulfur bioavailability.

Ascorbic acid and Iodine (I)

Iodine (I) is an essential constituent of the thyroid hormone tri-iodothyronine (T3) and thyroxine (T4) with plasma half lives of approximately 2 and 8 days, respectively. Iodine from the diet is absorbed in the gastrointestinal system.[91] Dietary iodine, before it is absorbed, is converted into the iodide ion, which is100% bioavailable and absorbed completely from food and water. In addition, it has been suggested that the effective utilization of iodine depends on a selenium containing enzyme, thus, we should be maintained adequate selenium status.[91]To the best of our knowledge, not much research has been conducted on iodine bioavailability and no recent researches studied the effect of ascorbic acid on iodine bioavailability.

Ascorbic acid and toxic metals (Mercury (Hg) and Cadmium (Cd)): Mercury (Hg) is a naturally occurring element that is found in water, air and soil. Exposure to mercury – even in very small amounts – may cause serious health complications and is a threat to the development of the child in utero and early in life.[95] Mercury is a common chemical exposure and environmental pollutant.[91] Mercury may have toxic effects on the digestive, nervous and immune systems, and on lungs, kidneys, skin and eyes. Neurological and behavioral disorders may be observed after inhalation, ingestion or dermal exposure of various mercury compounds.[95] Mercury is considered by WHO as one of the top ten chemicals or groups of chemicals of major public health concern. People are mainly exposed to methyl mercury, an organic compound.[95] Exposure mainly occurs through consumption of contaminated fish and shellfish that contain the compound.[91] Cadmium (Cd), a by-product of zinc production, is one of the most toxic elements to which human can be exposed in the environment. Once absorbed, cadmium is efficiently preserved in the human body and accumulates throughout the life.[96] Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells, the main accumulation site. Cadmium can also cause bone demineralization, either through direct bone damage or indirectly as a result of renal dysfunction. In the industry, excessive exposures to airborne cadmium may impair lung function and also increase the risk of lung cancer.[96] Cadmium does not play a role in higher biologic systems or human nutrition. Regular use of tobacco-containing products is a common route of cadmium exposure for smokers. The major source of cadmium exposure for nonsmokers is from the food supply in general, specially leafy vegetables.[91] Ouch or Itai‑Ita disease is unique to long term consumption of cadmium‑contaminated rice.[91] Cadmium and mercury are non-biodegradable toxic metals that may cause many harmful effects on the thyroid gland and blood. Vitamin C has been found to be a significant chain breaking antioxidant and enzyme co-factor against metal toxicity (cadmium and mercury).[97] Elmore[44] was reported a decreased intestinal cadmium uptake, and an increased cadmium transport in vitro in rat intestine treated with ascorbic acid, but ascorbic acid fails to affect the intestinal absorption of cadmium and mercury.[26]It was concluded that cadmium and mercury are toxic and tended to bioaccumulate in many organs and their toxic action can be submissive by vitamin C in biological systems.[97]To the best of our knowledge, not much research has been conducted on mercury and cadmium bioavailability and no recent researches studied the effect of ascorbic acid on mercury and cadmium bioavailability. Because they are toxic for human being.

CONCLUSION

Nutrient deficiency is related to nutrient bioavailability, by determining the enhancing and inhibiting factors, optimal nutrient bioavailability can be achieved. The mineral deficiency problem is still taking place in the developing countries regardless of the mineral deficiency intervention programs, thus the interest in enhancing the intake to achieve the optimal nutrition accompanied by food security has been lately highlighted. The advantages and disadvantages of nutrient interactions should be determined by systematic studies in order to promote the micronutrient status in different populations. Ascorbic acid supplementation enhance iron absorption and bioavailability, ascorbic acid is considered the most effective nonheme iron enhancer which can overcome the adverse effects from the inhibiting substances, the addition of ascorbic acid enhanced calcium's absorption, while ascorbic acid addition caused a suppression in copper intestinal absorption in animals. In regard to zinc, ascorbic acid recently found that its addition could enhance its bioavailability, ascorbic acid had an inhibitory effect on nickel absorption, neither the absorption of cadmium nor mercury. However, the effect of ascorbic acid on selenium's bio availability is quite varied depending on the type of ingested selenium compound, the addition of ascorbic acid to phosphorus did not significantly affect its utilization, but a decrease in manganese's absorption was seen upon ascorbic acid addition. There is no available data in regard to molybdenum, vanadium, silicon, sulfur and iodine interactions with ascorbic acid. The ascorbic acid addition did not have appreciable effect on cobalt's absorption, it affected slightly. There is no data available regarding the effect of ascorbic acid on reducing the bioavailability of potassium. Although some researchers found that magnesium bioavailability enhanced by Ascorbic acid, this effect on magnesium bioavailability still has no judgment.

Acknowledgement: Declared None

Funding and sponsorship: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Declaration of competing interest: The authors declare that they have no competing or conflict of interest.

Ethics policies: This research did not request ethical approval

Author contribution: All authors contributed to writing this review. All authors approved the final version to be published.

REFERENCES

1. Sandstrom B. Micronutrient interactions: Effects on absorption and bioavailability, *Br. J. Nutr.*2001; 85(S2): 181-185. https://doi.org/10.1049/BJN2000312
2. Hilton JW. The interaction of vitamins, minerals and diet composition in the diet of fish. *Aquaculture*. 1989;79(1-4):223-244. https://doi.org/10.1016/0044-8486(89)90463-8
3. Zafar N, Khan MA. Effects of dietary iron on growth, hematology, oxidative stress and hepatic ascorbic acid concentration of stinging catfish Heteropneustes fossilis. Aquaculture. 2019;734642. https://doi.org/10.1016/j.aquaculture.2019.734642
4. Smirnoff N. Ascorbic acid metabolism and functions: A comparison of plants and mammals. *Free Radica. Bio. and Med*. 2018;122:116-129.
5. Singh P, Prasad S. Determination of ascorbic acid and its influence on the bioavailability of iron, zinc and calcium in Fijian food samples. *Microchem. J.* 2018;139:119-124. https://doi.org/10.1016/j.microc.2018.02.019

6. Abdullah M, Attia FN. Vitamin C (ascorbic acid). *In Stat Pearls*. Stat Pearls Publishing. 2019.
7. Pinnell SR, Yang H, Omar M, et al., Topical L Ascorbic acid: percutaneous absorption studies. *Derma. surg*. 2001; 27(2):137-142. https://doi.org/10.1046/j.1524-4725. 2001. 00264.x
8. Sengupta M, Shaharyar MA, Rahman M, Anand K, Kundu A. Vitamin C Loaded Chemically Modified Nano Carrier for Human Health Care Application. *Curr. Biochem. Eng*. 2020; 6(1):34-40. https://doi.org/10.2174/2212711906666 190903113903
9. Jimenez-Aguilar DM, Grusak MA. Minerals, vitamin C, phenolics, flavonoids and antioxidant activity of Amaranthus leafy vegetables, *J. Food Comp. Anal*. 2017; 58: 33– 39. https://doi.org/10.1016/j.jfca.2017.01.005
10. Bertinato J, Hidiroglou N, Peace R, et al., Sparing effects of selenium and ascorbic acid on vitamin C and E in guinea pig tissues. *Nutr. J.* 2007; 6(1):7. https://doi.org/10.1186/ 1475-2891-6-7
11. Teucher B, Olivares M, Cori H. Enhancers of iron absorption: ascorbic acid and other organic acids. *Inter. J. Vit. Nutr. Res.* 2004;74(6), 403–419. https://doi.org/10. 1024/0300-9831.74.6.403
12. Du J, Cullen JJ, Buettner GR. Ascorbic acid: chemistry, biology and the treatment of cancer. *Biochim. Biophys. Acta.* 2012; 1826(2): 443–457. https://doi.org/10.1016/ j.bbcan.2012.06.003
13. Kim S, Chen J, Cheng T, et al., PubChem 2019 update: improved access to chemical data, Ascorbic acid. *Nucl Acids Res.* 2019; 47(D1):1102-1109. https://doi.org/ 10.1093/nar/gky1033
14. Gebicki JM, Nauser T, Domazou A, Steinmann D, Bounds PL, Koppenol WH. Reduction of protein radicals by GSH and ascorbate: potential biological significance. *Amino Acids*. 2010;39: 1131–1137.https://doi.org/10.1007/s00726-010-0610-7.
15. Imam MU, Zhang S, Ma J, Wang H, Wang F. Antioxidants mediate both iron homeostasis and oxidative stress. *Nutrients*.2017;9(7):671.https://doi.org/10.3390/nu9070671
16. Cho S, Chae JS, Shin H, et al., Enhanced Anticancer Effect of Adding Magnesium to Vitamin C Therapy: Inhibition of Hermetic Response by SVCT-2 Activation. Transla. Onco. 2020; 13(2):401-409. https://doi.org/10.1016/j.tranon. 2019.10.017
17. Colunga Biancatelli RML, Berrill M, Marik PE. The antiviral properties of vitamin C. *J.Exp. Rev. Anti-infec. Therap.* 2020; 18(2), 99-101. https://doi.org/10.1080/ 14787210.2020.1706483
18. Saul AW. Vitamin C Protects Against Coronavirus. *Orthomolecu. Org.* 2020. http://orthomolecular.org/ subscribe.html
19. Domazou AS, Koppenol WH, Gebicki JM.Efficient repair of protein radicals by ascorbate. *Free Radic. Biol. Med.*2009;46:1049–1057. https://doi.org/10.1016/j.freerad biomed.2009.01.001
20. Hanuka Katz I, Eran Nagar E, Okun Z, Shpigelman A. The Link between Polyphenol Structure, Antioxidant Capacity and Shelf-Life Stability in the Presence of Fructose and Ascorbic Acid. *Molecules*. 2020;25(1), 225.https://doi.org/ 10.3390/molecules25010225
21. De Tullio MC. 2012. Beyond the antioxidant: the double life of vitamin C. In: Stanger O. (eds) Water Soluble Vitamins. *Subcell. Biochem*. 2012; 56:49-65. https://doi. org/10.1007/978-94-007-2199-9_4
22. Singh P, Prasad S, Aalbersberg W. Bioavailability of Fe and Zn in selected legumes, cereals, meat and milk products consumed in Fiji, *Food Chem.*2016;207:125–131. https://doi.org/10.1016/j.foodchem.2016.03.029
23. Watzke HJ. Impact of processing on bioavailability examples of minerals in foods. *Tren. Food Sci. Tech.* 1998;9(8-9):320-327. https://doi.org/10.1016/S0924-2244 (98)00060-0
24. Adams W, Blust R, Dwyer R, et al., Bioavailability assessment of metals in freshwater environments: A historical review. *Envir.Toxico. Chem*. 2020;39(1):48-59. https://doi.org/10.1002/etc.4558
25. Upadhaya SD, Kim IH. Importance of micronutrients in bone health of monogastric animals and techniques to improve the bioavailability of micronutrient supplements: a review. *Asian-Australasian J. Anim. Sci.* 2020. https://doi.org/10.5713/ajas.19.0945
26. Solomons NW, Viteri FE. Biological interaction of ascorbic acid and mineral nutrients. *Adv. Chem.* 1982; 200:551–569. DOI: 10.1021/ba-1982-0200.ch023
27. Goyer RA. Toxic and essential metal interactions. *Annu. Rev. Nutr.* 1997; 17(1):37-50. https://doi.org/10.1146/ annurev.nutr.17.1.37
28. Schaeffer-Korbylo L, Won B, Maloney VP, Szewczyk G. Bioavailability of metal ions. Washington, DC: U.S. Patent and Trademark Office. 2020.
29. Knudsen E, Sandström B, Solgaard P. Zinc, copper and magnesium absorption from a fibre-rich diet. *J. Trace Elem. Med. Bio*. 1996;10(2):68-76.https://doi.org/10.1016/ S0946-672X(96)80014-9
30. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. *J. Res. Med. Sci.* 2014;19(2):164-174.
31. Monsen ER. Iron nutrition and absorption: dietary factors which impact iron bioavailability. *J. Amer. Diet. Assoc.* 1988; 88(7):786-790. PMID: 3290310.
32. Lynch SR. Cook JD. Interaction of vitamin C and iron. *Annal. New York Acad. Sci*. 1980; 355(1):32-44.
33. Dias DM, Costa N, Nutti MR, Tako E, Martino HSD. Advantages and limitations of in vitro and in vivo methods of iron and zinc bioavailability evaluation in the assessment of biofortification program effectiveness. *Crit. Rev. Food Sci. Nutr.* 2018; 58(13):2136-2146. https://doi.org/10.1080/ 10408398.2017.1306484
34. Kumar S, Anukiruthika T, Dutta S, Kashyap AV, Moses JA, Anandharamakrishnan C. Iron deficiency anemia: A comprehensive review on iron absorption, bioavailability and emerging food fortification approaches. *Tren. Food Sci. Tech*. 2020;99:58-75. https://doi.org/10.1016/j.tifs. 2020.02.021
35. Pauline M, Verghese ST, Srinivasu BY, et al., Effect of ascorbic acid rich, micro-nutrient fortified supplement on the iron bioavailability of ferric pyrophosphate from a milk-based beverage in Indian school children. *Asia Pacific J. Clin.Nutr*. 2018; 27(4):792-796.
36. Gautam S, Platel K, Srinivasan K.Influence of combinations of promoter and inhibitor on the bioaccessibility of iron and zinc from food grains. *Intern. J. Food Sci. Nutr*. 2011; 62:826-834. https://doi.org/10. 3109/09637486.2011.584861
37. Villano D, Vilaplana C, Medina S, et al., Relationship between the ingestion of a polyphenol-rich drink, hepcidin hormone, and long-term training. *Molecules*. 2016; 21(10):1333. https://doi.org/10.3390/molecules21101333

38. Amalraj A, Pius A. Relative contribution of oxalic acid, phytate and tannic acid on the bioavailability of calcium from various calcium salts-an in vitro study. *Intern. Food Res. J.* 2017; 24(3):1278-1285. http://agris.upm.edu.my:8080/dspace/handle/0/15010
39. FAO, & WHO. Vitamin and mineral requirements in human nutrition (Second edition ed.). Italy: Rome. 2004.
40. Poneros AG. Erdman JW. Bioavailability of calcium from tofu, tortillas, nonfat dry milk and mozzarella cheese in rats: Effect of supplemental ascorbic acid. J. Food Sci. 1988;53(1):208-210.https://doi.org/10.1111/j.1365-2621.1988.tb10210.x
41. Sandstorm B, Cederblad A. Effect of ascorbic acid on the absorption of zinc and calcium in man.*Int. J. Vitam. Nutr. Res.*1987; 57:87-90. PMID: 3583599
42. Mehansho H, Kanerva RL, Hudepohl GR, Smith KT. Calcium bioavailability and iron-calcium interaction in orange juice. *J. Amer. Coll. Nutr*. 1989:8(1):61-68. https://doi.org/10.1080/07315724.1989.10720278
43. Pisoschi AM, Danet AF, Kalinowski S. Ascorbic acid determination commercial fruit juice samples by cyclic voltammetry. *J. Autom. Methods Manag. Chem.* 2008; 2008: 1–8. doi:10.1155/2008/937651
44. Elmore AR. Final report of the safety assessment of L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as used in cosmetics. *Intern. J. Toxico*. 2005; 24(2):51-111. DOI: 10.1080/10915810590953851
45. Zeid CA, Yi L, Kaler SG.Copper Metabolism and the Liver. *The Liver: Bio. Pathobio*. 2020; 207-214. https://doi.org/10.1002/9781119436812.ch18.
46. Wapnir, R. A. (1998). Copper absorption and bioavailability. *Amer.J.Clin.Nutr.* 1998;67(5):1054S-1060S. https://doi.org/10.1093/ajcn/67.5.1054S
47. Platel K, Srinivasan K. (2016). Bioavailability of micronutrients from plant foods: an update. *Crit.Rev.Food Sci. Nutr.* 2016;56(10):1608-1619. https://doi.org/10.1080/10408398.2013.781011
48. Johnson PE, Korynta ED. Effects of copper, iron, and ascorbic acid on manganese availability to rats. *Proce. Soci. Experi. Bio. Med.* 1992; 199(4), 470-480. https://doi.org/10.3181/00379727-199-43383.
49. Van den Berg GJ, Yu S, Lemmens AG, Beynen AC. Ascorbic acid feeding of rats reduces copper absorption, causing impaired copper status and depressed biliary copper excretion. *Bio. Trac. Elem. Res.* 1994; 41(1-2):47. https://doi.org/10.1007/BF02917216
50. Hambidge KM, Miller LV, Westcott JE, Sheng X,Krebs NF. Zinc bioavailability and homeostasis. *Amer. J. Clin. Nutr*. 2010:91(5):1478S-1483S. https://doi.org/10.3945/ajcn.2010.28674I
51. Ramírez-Cárdenas L, Leonel AJ, Costa NB, Reis FP. (2010). Zinc bioavailability in different beans as affected by cultivar type and cooking conditions. *Food Res. Intern*. 2010; 43:573-581.https://doi.org/10.1016/j.foodres.2009.07.023.
52. Kies C, Young E, Mcendree L. Zinc bioavailability from vegetarian diets. *NutrBioavai. Zinc*. 1983;210:115-126. DOI: 10.1021/bk-1983-0210.ch008
53. Solomons NW, Jacob RA, Pineda O, Viteri FE. Studies on the bioavailability of zinc in man III: Effects of ascorbic acid on zinc absorption. *Amer. J. Clin.Nutr*. 1979; 32(12): 2495–2499. https://doi.org/10.1093/ajcn/ 32.12.2495
54. Etcheverry, Wallingford, &Glahn. The effect of calcium salts, ascorbic acid and peptic pH on calcium, zinc and iron bioavailability's from fortified human milk using an in vitro digestion/Caco-2 cell model. *Intern. J. Vit. Nutr. Res.* 2005; 75(3):171-178. DOI: 10.1024/0300-9831.75.3.171
55. KappelerD, Heimbeck I, Herpich C, Naue N, Höfler J, Timmer W, Michalke B. Higher bioavailability of magnesium citrate as compared to magnesium oxide shown by evaluation of urinary excretion and serum levels after single-dose administration in a randomized cross-over study. *BMC Nutr*. 2017:3(1), 7. https://doi.org/10.1186/s40795-016-0121-3
56. Laurin LP, Leblanc M. Disorders of potassium and magnesium. *In Crit.Care Nephro*. 2019:339-344. https://doi.org/10.1016/B978-0-323-44942-7.00057-1
57. Blancquaert L, Vervaet C, Derave W. Predicting and Testing Bioavailability of Magnesium Supplements. *Nutrients*. 2019; 11(7): 1663. https://doi.org/10.3390/nu11071663
58. Fine KD, Santa-Ana CA, Porter JL, Fordtran JS. Intestinal absorption of magnesium from food and supplements. *J. Clin. Investig.* 1991; 88(2):396-402. DOI: 10.1172/JCI115317
59. Dualé C, Cardot JM, JoannyF, et al., An advanced formulation of a magnesium dietary supplement adapted for a long-term use supplementation improves magnesium bioavailability: in vitro and clinical comparative studies. *Bio. Trace Elem. Res*. 2018; 186(1):1-8. https://doi.org/10.1007/s12011-018-1277-2
60. European Food Safety Authority (EFSA). Calcium ascorbate, magnesium ascorbate and zinc ascorbate added for nutritional purposes in food supplements. *EFSA Journal*. 2009;7(3):994. https://doi.org/10.2903/j.efsa.2009.994
61. Etcheverry P, Grusak MA., Fleige LE. Application of in vitro bio accessibility and bioavailability methods for calcium, carotenoids, folate, iron, magnesium, polyphenols, zinc, and vitamins B6, B12, D, and E. *Frontiersphysio*.2012;3:317.https://doi.org/10.3389/fphys.2012.00317
62. Njoumi S, Bellagha S, Icard-Vernière C, Picq C, Amiot MJ, Mouquet-Rivier C. Effects of cooking and food matrix on estimated mineral bioavailability in Mloukhiya, a Mediterranean dish based on jute leaves and meat. *Food Res. Intern*. 2018; 105:233-240. https://doi.org/10.1016/j.foodres.2017.11.020
63. Danzeisen R, Williams DL, Viegas V, Dourson M, Verberckmoes S, Burzlaff A. (2020). Bioelution, Bioavailability, and Toxicity of Cobalt Compounds Correlate. *Toxico. Sci.* 2020;174(2):311-325. https://doi.org/10.1093/toxsci/kfz249
64. Valberg LS, Ludwig J, Olatunbosun D. Alteration in cobalt absorption in patients with disorders of iron metabolism. *Gastroenterology*.1969;56(2):241-251. https://doi.org/10.1016/S0016-5085(69)80123-X
65. Solomons NW, Viteri F, Shuler TR, Nielsen FH. Bioavailability of Nickel in Man: Effects of Foods and Chemically Defined Dietary Constituents on the Absorption of Inorganic Nickel. *J.Nutr.* 1982;112(1):39-50. https://doi.org/10.1093/jn/112.1.39
66. Afolaranmi, G. A., and Helen Grant, M. The effect of ascorbic acid on the distribution of soluble Cr and Co ions in the blood and organs of rats. *J. Appl.Toxico*. 2011;33(3):220–226. https://doi.org/10.1002/jat.1744

67. Yildirim O, Buyukbingol Z. Effects of Supplementation with a Combination of Cobalt and Ascorbic Acid on Antioxidant Enzymes and Lipid Peroxidation Levels in Streptozocin-Diabetic Rat Liver. *Biol. Trace Elem. Res*. 2002;90(1-3):143–154.https://doi.org/10.1385/BTER:90:1-3:143
68. Das KK, Büchner V. Effect of nickel exposure on peripheral tissues: Role of oxidative stress in toxicity and possible protection by ascorbic acid. *Rev. on Enviro. Health*. 2007;22(2):133-149.
69. Das KK, Das SN. Studies on the Role of Ascorbic Acid in Nickel Induced Hepatic Nucleic Acid Concentrations in Rats. *J. BasicClin. Physio Pharmaco*. 2004;15(3-4):185-195.
70. Kadi IE, Dahdouh F. Vitamin C pretreatment protects from nickel-induced acute nephrotoxicity in mice. *ArchIndus. Hygi. Toxico*. 2016;67(3):210-215. https://doi.org/10.1515/aiht-2016-67-2753
71. Salnikow K, Kasprzak KS. Ascorbate Depletion: A Critical Step in Nickel Carcinogenesis? *Enviro. Health Persp*. 2005;113(5):577-584. https://doi.org/10.1289/ehp.7605
72. Kasprzak KS, Diwan BA, Kaczmarek MZ, Logsdon, DL, Fivash MJ, Salnikow K. Effects of ascorbic acid on carcinogenicity and acute toxicity of nickel subsulfide, and on tumor transplants growth in gulonolactone oxidase knock-out mice and wild-type C57BL mice. *Toxico. Appl. Pharmaco*. 2011;257(1), 32–37. https://doi.org/10.1016/j.taap.2011.08.015
73. Rai, L. C., & Raizada, M. Toxicity of nickel and silver to Nostocmuscorum: Interaction with ascorbic acid, glutathione, and sulfur-containing amino acids. *Ecotoxico. Enviro. Safety*. 1987;14(1):12-21.https://doi.org/10.1016/0147-6513(87)90078-9
74. Gupta AD, Dhundasi SA, Ambekar JG, Das KK. Effect of 1-ascorbic acid on antioxidant defense system in testes of albino rats exposed to nickel sulfate. *J. Basic Clin. Physio. Pharmaco*. 2007;18(4):255-266.
75. Das S, Reddy RC, Chadchan KS, Patil AJ, BiradarMS, Das KK. Nickel and Oxidative stress: Cell Signaling Mechanisms and Protective Role of Vitamin C. *Endocr. Metabo.Immune.Disord. drug targets*.2019;20:1-8. DOI: 10.2174/1871530319666191205122249
76. Sivaram AG, Suresh MV, Indira M. Combined effect of ascorbic acid and selenium supplementation on alcohol-induced oxidative stress in guinea pigs. Comparative Biochemistry and Physiology Part C: *Toxico. Pharmaco*. 2003;134(3):397-401. https://doi.org/10.1016/S1532-0456(03)00009-7
77. Vitamin C Can Promote Selenium Utilization. *Nutr. Rev.* 2009; 48(7):290-291.
78. Martin RF, Young VR, Blumberg J, Janghorbani M. (1989). Ascorbic acid-selenite interactions in humans studied with an oral dose of 74Se032-. *Amer. J. Clin.Nutr.* 1989;49(5):862-9. https://doi.org/10.1093/ajcn/49.5.862
79. Robinson MF, Thomson CD,Huemmer PK. (1985). Effect of a Megadose of Ascorbic Acid, a Meal and Orange Juice on the Absorption of Selenium as Sodium Selenite. *NewZeland Med J.* 1985; 98 (784):627-629. PMID: 3861972
80. Mutanen M, Mykkänen HM. Effect of ascorbic acid supplementation on selenium bioavailability in humans Human nutrition. *Clin.Nutr.* 1985;39(3):221-226. PMID: 4019267
81. Jacques-Silva MC, Nogueira CW, Broch LC, Flores EM, Rocha Note JBT. Diphenyl Diselenide and Ascorbic Acid Changes Deposition of Selenium and Ascorbic Acid in Liver and Brain of Mice. *Pharmaco. Toxico*. 2001;88(3):119-125. https://doi.org/10.1034/j.1600-0773.2001.d01-92.x
82. Novotny, J. A., & Milner, J. A. Impact of ascorbic acid on selenium-induced growth inhibition of canine mammary tumor cells in vitro. *J.Nutr. Biochem.* 1993;4(6):341-345. https://doi.org/10.1016/0955-2863(93)90079-C
83. Fairweather-Tait SJ, Collings R, Hurst R. Selenium bioavailability: current knowledge and future research requirements.*Amer. J.Clin.Nutr.* 2010;91(5):1484S–1491S. https://doi.org/10.3945/ajcn.2010.28674J
84. Calvo MS1, Lamberg-Allardt CJ2. Phosphorus. American Society for Nutrition. *Adv.Nutr.* 2015;6:860-862.
85. Ke G, Huang J, Zhu Y, et al., Effect of Ascorbic Acid on Mineral and Bone Disorders in Hemodialysis Patients: a Systematic Review and Meta-Analysis. *Kidney Blood Pressu. Res*. 2018;43(5):1459-1471. https://doi.org/10.1159/000493661
86. Chen P, Bornhorst J, Aschner M. Manganese metabolism in humans. *Universität Potsdam*. 2019;711:25. https://doi.org/10.25932/publishup-42743
87. Davidsson L, Cederblad A, Lönnerdal BO, Sandström B. The effect of individual dietary components on manganese absorption in humans. *Amer.J.Clin.Nutr.* 1991;54(6):1065-1070.https://doi.org/10.1093/ajcn/54.6.1065
88. Davidsson L, Almgren A, Juillerat MA, Hurrell RF. Manganese absorption in humans: the effect of phytic acid and ascorbic acid in soy formula. *Amer. J. Clin. Nutr.* 1995;62(5):984-987.https://doi.org/10.1093/ajcn/62.5.984
89. Stone MS, Martyn L, Weaver CM. Potassium intake, bioavailability, hypertension, and glucose control. *Nutrients.* 2016;8(7):444. https://doi.org/10.3390/nu8070444
90. Schwarz G, Mendel RR,Ribbe MW. Molybdenum cofactors, enzymes, and pathways. *Nature*. 2009; 460(7257), 839-847.https://doi.org/10.1038/nature08302
91. Mehri, A. (2020). Trace elements in human nutrition (ii)– An update. *Intern. J. Preven. Med.* 2020;11(1):2-17. DOI: 10.4103/ijpvm.IJPVM_48_19
92. Rehder D. Vanadium. Its role for humans. In Interrelations between essential metal ions and human diseases. *Biol Trace Elem Res*.2013;13:139-169. https://doi.org/10.1007/978-94-007-7500-8_5.
93. Van Dyck K, Robberecht H, Van Cauwenbergh R, Van Vlaslaer V, Deelstra H. Indication of silicon essentiality in humans. *Biol Trace Elem Res*. 2000;77(1):25-32. https://doi.org/10.1385/BTER:77:1:25
94. Ozbek N, Akman S. Determination of total sulfur in food samples by solid sampling high-resolution continuum source graphite furnace molecular absorption spectrometry. *J.Agri.Food Chem.* 2013;61(20):4816-4821.https://doi.org/10.1021/jf4009263.
95. WHO, https://www.who.int/news-room/fact-sheets/detail/mercury-and-health, 2017.
96. Bernard A.Cadmium & Its Adverse Effects on Human health. *Indian J. Med. Res*. 2008;128(4):557-64.
97. Khan R, Ali S, Mumtaz S, et al., Toxicological effects of toxic metals (cadmium and mercury) on blood and the thyroid gland and pharmacological intervention by vitamin C in rabbits. *Enviro. Sci. Poll. Res.* 2019; 26, 16727–16741. https://doi.org/10.1007/s11356-019-04886-9.

****