

# Vitamin C: Evolution, Prehistory, and History

Moacir C. Andrade Jr.\*

Department of Nutrition and Metabolic Disorders, Faculty of Medicine, Instituto Metropolitano de Ensino (IME), Manaus, Brazil  
\*Corresponding author: [moacircoutjr@gmail.com](mailto:moacircoutjr@gmail.com)

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**Abstract** Normal metabolism ensures the adequate use of nutrients. Enzymes are the most important mediators of metabolism. Vitamin C, also identified as L-ascorbic acid (or L-ascorbate), is an important enzyme cofactor, playing other significant physiological roles in the human organism. During evolution, a few species, including the *Homo sapiens*, lacked L-gulonolactone oxidase (recommended name), L-gulono-1,4-lactone oxidase (a synonym), i.e., the enzyme that catalyzes the last step of vitamin C biosynthesis. Hereafter, vitamin C is an essential micronutrient for humans and its deficiency (or scurvy) may be fatal. Indeed, scurvy has plagued humankind since prehistoric times. Nevertheless, the industry began producing vitamin C in the early 1930s. Scientific interest in vitamin C became popular thanks to the eminent American chemist Linus Carl Pauling (1901-1994), who helped to spread the vitamin benefits worldwide, especially toward viral infections (e.g., common cold and flu). The COVID-19 pandemic has renewed the interest in vitamin C, opening new perspectives in the vitamin research and potential therapeutic uses. New conceptual elements have emerged, allowing the elucidation of points related to the evolution, prehistory, and history of vitamin C, and motivating the present review article.

**Keywords:** ascorbic acid, evolution, history, humans, prehistory, pseudogenes, scurvy

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## 1. Evolutionary Aspects of Vitamin C

Unlike paleontologists, biologists cannot use fossil evidence per se to investigate the evolution of complex organic compounds such as water-soluble vitamins, especially vitamin C, but the conservation of these molecules among living species can give clues to evolutionary changes [1].

At this regard, pseudogenes, defined as nonfunctional (or noncoding) sequences of genomic deoxyribonucleic acid (DNA), and originally derived from functional genes, may be considered the equivalents of genomic fossils [2,3,4,5,6,7]. As such, pseudogenes serve as valuable tools for studying the dynamics and evolution of genes and genomes (the pertinent aspects of vitamin C are reviewed ahead) [3,4,5].

Vitamin C is an essential (or indispensable) nutrient for anthropoid primates, including humans, among other species. As a reminder, essential nutrients cannot be synthesized by the human organism and must be provided by the diet, including: (i) ten amino acids (arginine during growth, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine); (ii) two polyunsaturated fatty acids (linoleic and  $\alpha$ -linolenic acids); (iii) most vitamins (except vitamin B3 (or niacin) and vitamin D that can be synthesized by humans); (iv) and all minerals [7,8,9,10,11].

Humans are, therefore, among the few species who cannot synthesize vitamin C, gaining it from the daily diet.

Vitamin C is crucial for human physiology, for instance, for the absorption and metabolism of iron, antioxidant activity, collagen synthesis (**subsection 3.1.**), and stimulation of immune process (**subsection 3.6.**) [12,13]. Vitamin C deficiency (or scurvy) presents with particular clinical manifestations according to age groups (i.e., children, adults, and the elderly) and may lead to death without the mandatory adequate supplementation [13].

Briefly, on genetic and biochemical bases, two large groups of single-celled microorganisms can be differentiated and have diverged early in evolution: the Archaea and Bacteria, whose members are prokaryotes as described below [14]. Eukaryotes (e.g., fungi, plants, animals, and humans), which make up the third domain (Eucarya), evolved from the same branch that gave rise to the Archaea (hence eukaryotes are more closely related to Archaea than Bacteria), and are discussed below as well [14].

Prokaryotes such as bacteria are the oldest existing life form on Earth [15]. They are unicellular microorganisms, lacking a distinct nucleus and other membrane-bound organelles [16,17]. In contrast, most eukaryotes are multicellular organisms (although several are unicellular microorganisms such as fungi and the *Leishmania* protozoan parasites) [18,19,20]. A membrane-bound nucleus characterizes eukaryotes and, among other features, a microtubule cytoskeleton that serves to separate chromosomes during mitosis (or nuclear division) [21,22,23].

Prokaryotes do not synthesize vitamin C neither need it to be supplied, so the particular vitamin functions that are essential for mammals and plants are unnecessary or are replaceable by other compounds [24].

Conversely, most eukaryotes synthesize vitamin C, while yeast and fungal cells (e.g., *Saccharomyces cerevisiae* and *Candida albicans*, respectively), as a substitute, usually produce D-erythroascorbic acid (D-EAA), an isomeric five-carbon analog whose significance is not yet sure (although it could serve as an antioxidant, potentially aiding fungal survival in the presence of oxidative stress induced by the host) [24,25,26,27,28]. Nonetheless, microorganisms such as the baker's yeast *S. cerevisiae* are versatile, and under suitable conditions, can synthesize vitamin C via the pathway naturally used for D-EAA biosynthesis [29,30].

Furthermore, eukaryotes such as plants synthesize vitamin C and vitamin E (or  $\alpha$ -tocopherol) in abundance and are also rich in polyphenolic compounds (among which flavonoids make up the most important single group) [30,31]. These substances have strong antioxidant properties [30,31]. In fact, antioxidant molecules are necessary for aerobic organisms like plants and humans (see additional discussion below).

Most insects that feed on green plants need vitamin C to develop, but authors suggest some species forgo the vitamin or either synthesize it de novo or depend on symbiotic organisms [32]. Moreover, a study showed the potential role of antioxidant diet (vitamin C intake) in adaptive genome responses, and thus on the pesticide resistance evolution within insect populations (e.g., the fruit fly *Drosophila melanogaster*) [33].

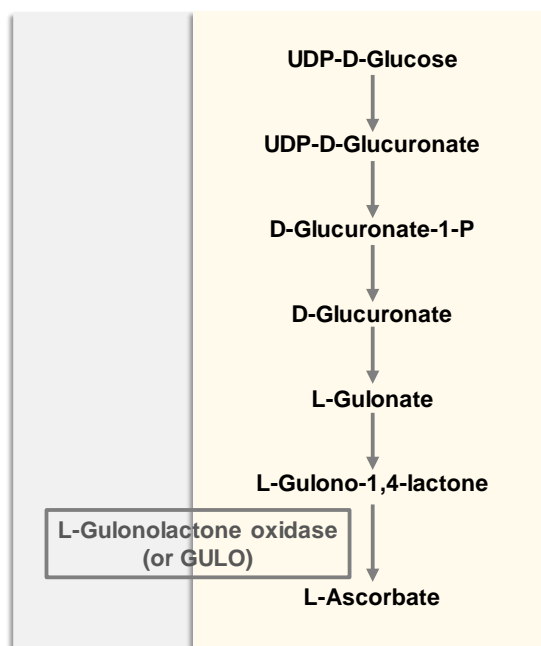
Galliform birds synthesize vitamin C in the kidneys [34]. This endogenous synthesis may present a limit in young birds (whose supplementation with vitamin C remains controversial) [35]. However, certain bird species (genera of Passeriformes) have lost the ability to synthesize vitamin C in different organs (i.e., either in the kidneys only or in the kidneys and liver, or in the liver only, or even in no organ) [10]. Other vertebrates unable to synthesize vitamin C comprise teleost fishes, additional anthropoid primates, guinea pigs, and bat species [10,36].

In vertebrates, the inability to synthesize vitamin C is due to random mutations in the *GULO* gene, which encodes the eponymous enzyme responsible for catalyzing the last step of vitamin C biosynthesis (Figure 1) [10] [36,37,38,39].

Nishikimi and Yagi (1991) sequenced the rat *GULO* gene, then used this gene sequence to probe the genomes of other species [37,38]. The human genome was proven to have a nonfunctional *GULO* pseudogene that is homologous to the functional rat *GULO* gene (Figure 2) [37,38,44].

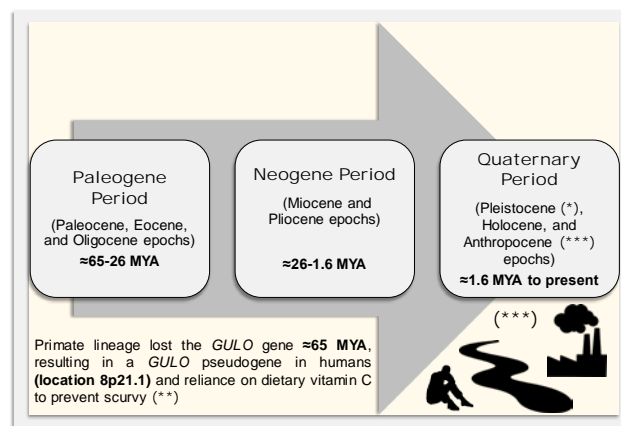
Primitive man's diet underwent important changes, in sum, from predominant carnivorous diet in the early and middle Pleistocene (animal flesh could provide enough vitamin C to prevent scurvy) to seasonal omnivorous diet (both plants and meat) in the end of the Pleistocene, ensuring availability of the micronutrient and compensating for its lack of biosynthesis [56].

It is worth remarking that oxygen free radicals are byproducts of normal metabolism and their formation is not problematic as long as a balance between production and excretion occurs [57]. Free radicals play a role in the toxicity of chemicals [58]. Strong natural antioxidants, such as the abovementioned vitamins C and E and flavonoids, scavenge and neutralize free radicals, preventing oxidative damage to cellular components [31,59].



\*: adapted from [39]. UDP: uridine diphosphate. In this scheme, the metabolic pathways were simplified, highlighting only the final defective enzymatic step. It is important to note that photosynthetic protists, generally referred to as algae (chlorophyll-bearing eukaryotes), have enzymatic components from animal and plant pathways [22,39,40]. In plants and almost all photosynthetic eukaryotes, the final step of vitamin C biosynthesis is predominantly catalyzed by L-galactonolactone dehydrogenase [39] [41,42,43].

Figure 1. Vitamin C biosynthesis in animals\*



≈: almost equal to. MYA: million years ago. (\*): the *Homo sapiens*, formally established as a species by the Swedish taxonomist Carl von Linnæus (1707-1778) in 1758, may have emerged in Africa ≈200,000 years ago [49-51]. (\*\*): the human *GULO* pseudogene is on the short arm of chromosome 8 [52]. (\*\*\*) the Anthropocene may be defined as the current epoch in which humans have been having large influence over the status and trajectory of earth's climate and environment [53]. Nevertheless, this illustration also depicts what is more apparent from man's actions on nature since the start of the British Industrial Revolution (mid-18th century of the Christian Era or CE), i.e., pollution, disfiguration of landscapes, and anthropogenic climate change, as if humans evolved genetically and culturally to be unsustainable [54,55].

Figure 2. *GULO* pseudogene in humans [45,46,47,48]

Interestingly, with the increase of fresh water eutrophication (i.e., areas where the concentration of nitrate exceeds  $1 \text{ mg NO}_3\text{-N l}^{-1}$ ) and global warming, vitamin C helps turtle species in coping with stressful factors (e.g., hypoxia, anoxia) in harsh environments

during their hibernation [60,61,62].

Actually, the evolution of vertebrates from the aquatic medium to the terrestrial atmosphere (with a high concentration of environmental oxygen) was marked by tissue-specific expression of the *GULO* gene [63]. The mechanisms of oxygen-sensing and epigenetic control (i.e., a regulation independent of the DNA sequence itself) constitute new findings on the multifaceted biological role of vitamin C [64,65].

Uric acid is a strong antioxidant molecule too, but its major (pathophysiological) importance lies in its potential accumulation in the body, triggering chronic hyperuricemia, gout (the most common form of inflammatory arthritis by the deposition of monosodium urate crystals in the joints), and constituting a cardiovascular risk factor [66,67]. Humans also lack factor-independent urate hydroxylase (recommended name) or urate oxidase (a synonym), or simply UOX, i.e., an endogenous enzyme existent in most mammals that converts uric acid to allantoin (a highly soluble metabolite readily excreted by the kidneys) [68,69]. The human *UOX* pseudogene is on the short arm of chromosome 1 (1p22) and its formation can be attributed to several mutations during evolution [46,70].

The present work does not delve into the applicability of the “resurrected” human-source UOX, i.e., an enzyme with high uricolytic activity and stability [70]. The implications of the loss of this enzyme activity in the intermediary metabolism are also outside the realm of this work. However, it should be noted that the loss of UOX activity took place 20-30 MYA, independently from the earlier loss of vitamin C biosynthesis ability in primates (≈65 MYA), as pointed out in Figure 2 [48].

## 2. Tracking Back Vitamin C in Prehistoric Times

In general, prehistory is divided into periods that are called by the name of the major material used at the time such as the Stone Age, the Bronze Age, and the Iron Age [71]. The Stone Age, in its turn, is divided in three archeological periods, i.e., the Paleolithic (≈12,000-9500 before the Christian Era or BCE), the Mesolithic (≈9500-4000 BCE), and the Neolithic (≈4000-1700 BCE), ending up with the advent of literacy in ancient civilizations [45] [72,73,74].

Ancient civilizations such as the Greek, the Mesopotamian, and the Egyptian emerged in the Bronze Age, while civilizations such as the Phoenician in the Iron Age, and are discussed in subsection 3.1. [75].

The primary goal of Paleolithic and Mesolithic men was probably to gather all available resources to obtain calories for immediate survival, soon learning that vegetables were also necessary (but without correlating vegetable shortage in winter with consequent deficiencies of vitamin C and iron) [76]. In these pre-agricultural times, the meat of large mammals (e.g., mammoth, rhinoceros, and bison) was the major energy source along with that of vitamin C (as mentioned before) [77,78,79].

The Neolithic period is known for its groundbreaking developments in animal and crop domestication, specifically cereals and the emergence of agriculture

[80,81]. It changed the hunter-gatherer diet (plentiful in red meat and more bioavailable heme iron) to the cereal grain diet (with a predominance of the less bioavailable nonheme iron); this dietary shift resulting in an increased incidence of iron deficiency anemia and applying to the common mutation (*C282Y*) of the Homeostatic Iron Regulator (*HFE*) gene, related to hereditary hemochromatosis (or primary iron overload), thus representing an adaptation to the decreased dietary iron during this period (the *HFE* gene is on the short arm of chromosome 6 (6p21.3) and controls intestinal iron absorption and deposition in the tissues) [46] [82,83,84,85,86].

As referred to above, vitamin C impacts both on iron absorption and metabolism, and the lower incidence of this mutation in agrarian regions such as the Mediterranean and the Near East might have resulted from higher dietary intakes of iron owing to vitamin C abundant sources [12,83].

Archeological evidence of vitamin C deficiency can be found in prehistoric times. An analysis of periosteal lesions from commingled human remains at the Xaghra Circle hypogeum (i.e., an underground burial chamber) revealed the first case of probable scurvy from Neolithic Malta [87].

## 3. Vitamin C Throughout History

In contrast to prehistory, where archeological periods are determined by material usage, history may be divided into diverse periods based on impactful events that transformed entire civilizations or even the world, as further discussed below.

### 3.1. Ancient History

Ancient history studies encompass the civilizations of the oriental antiquity, such as the Egyptian, the Mesopotamian, the Hebrew, and the Phoenician, as well as the classic antiquity, which comprises the Greek and the Roman civilizations [55].

The German Egyptologist Georg Ebers (1837-1898) discovered an ancient papyrus at Thebes in the second half of the 19th century (1872), henceforth called by his name [88,89]. The Ebers papyrus is considered the most comprehensive medical papyrus ever recovered, dating back to 1534 BCE and revealing primordial commentaries on scurvy, such as major symptoms (e.g., bleeding gums and petechial hemorrhages) [90,91,92].

In ancient Mesopotamia, scurvy was known as “the evil smelling disease”, being classified in the therapeutic texts with disorders of the teeth [93].

The issue of scurvy was also discussed in biblical verses [94]. Of note, pomegranate (*Punica granatum* L., Lythraceae), whose fruits contain vitamin C (e.g., 6.2 mg/100 mL juice at harvest), is one of the seven food staples of the land of Israel mentioned in the Old Testament [95,96]. It originated from the regions now occupied by Iran and Afghanistan, and was brought to the Mediterranean countries by the Phoenicians (but the Egyptians are famous for having cultivated it around 2500 BCE) [95].

The Greek physician Hippocrates (460-370 BCE) termed scurvy *ileos emantis* to refer to a condition where the gums detach from the teeth and blood runs from the nostrils [97]. It is considered the first formal description of the disease [98].

Strabo (63 or 64 BCE–24 CE) was a Greek geographer who described the emergence of an epidemic of scurvy among the Roman troops in Arabia during the reign of Gaius Aelius Gallus, a Roman prefect [98,99].

In total, the clinical presentation of scurvy throughout the ancient history underscores the significance of oral and bleeding manifestations of this disease. In effect, vitamin C deficiency results in faulty collagen synthesis, which increases vascular fragility, bleeding tendency, and the related clinical signs [13].

### 3.2. Middle Ages

The Middle Ages began with the downfall of the Western Roman Empire (456 CE), subsisting until the conquest of Constantinople by the Ottoman Turks (1453) [55]. In this long historic corridor of almost a thousand years, the Crusades stand out as an example of religion used to justify war [100]. The Crusades occurred between the 11th and 14th centuries [101]. However, more Crusaders succumbed from scurvy than from fighting battles [102].

### 3.3. Modern History

The modern history started in the 15th century, and the date of 1492 (discovery of America) is a landmark for its beginning [55]. The first outbreak of sea scurvy was recorded during the Portuguese expedition to India (1497-1499) headed by Vasco da Gama (1469-1524), and more than half of his crew died from scurvy on this trip around the Cape of Hope (although the etiology of the deaths was entirely inexplicable at that point) [103,104,105].

These tragic outbreaks of sea scurvy would unfortunately repeat in history, as discussed below.

### 3.4. Contemporary History

Usually, the French Revolution (1789-1799) is used as a milestone to mark the beginning of the contemporary history [55]. Despite that, this and all the aforementioned pivotal events are not directly applicable to the historic demarcation of every known civilization. For instance, the medieval period in Denmark began with the end of the Viking Age in 1050 and came to a close in the mid-16th century [106].

The Napoleonic Age began during the French Revolution and ended in the renowned battle of Waterloo in 1815 [55]. But, according to Bhattacharyya et al., what was really behind the defeat of the French Forces against a healthier British Navy during their constant war, was the proper use of fresh lime juice (e.g., 0.35 g/L of vitamin C), then proposed by Sir James Lind (1716-1794), a Scottish surgeon in the Royal Navy, to help fight the scourge (scurvy) [14] [107,108,109].

In fact, in the mid-18th century, James Lind demonstrated that the juice of fresh citrus fruits cures scurvy [110,111]. However, until the end of the 18th

century, vitamin C was often unreachable in the dried foods and other food supplies stored for winter or for extended travels [14]. As a result, scurvy was a common disease in the world's navies and sailors until the beginning of the 19th century [112].

At this time, Axel Holst (1860-1931), professor of hygiene and bacteriology at the University of Oslo, and the pediatrician Theodor Frølich (1870-1947), were interested in a disease called ship beriberi (vitamin B1 or thiamine deficiency), which tormented the crews of sailing ships, showing an uncanny similarity to scurvy [113]. These two investigators suspected a nutritional deficiency, establishing an animal model (the abovementioned guinea pig, a non-synthesizer of vitamin C) that allowed a systematic study of factors that led to the disease and the preventive value of different substances [113]. Their findings were published at the beginning of the 20th century (1907), but caused scientific upheaval since the concept of nutritional deficiencies was an innovation at the time [113].

The Polish biochemist Casimir Funk (1884-1967) coined the term vitamin in 1912 for a substance that appeared to be vital to life, although it was not an amine, but the term was already enshrined and persisted without change (Latin *vita* + amine) [114,115,116,117]. A vitamin is an organic micronutrient existing in minute amounts in natural foodstuffs, indispensable to normal metabolism, whose lack in the diet may cause deficiency disease [114,116,117].

The Hungarian biochemist Albert von Szent-Györgyi (1893-1986) isolated vitamin C in the late 1920s, becoming the winner of the 1937 Nobel Prize in Physiology or Medicine [107,110,118].

The industrial production of vitamin C started in 1934 and was widely based on the Tadeus Reichstein (1897-1996) and Andreas Grüssner process, combining one-step bacterial fermentation with chemical conversions (now, the production is almost exclusively based on a two-step fermentation process, which reduces the chemical conversion stages) [119,120,121,122].

At the present time, around half of global vitamin C production is allocated for vitamin supplements, while the rest is used as a food additive (25%), in beverage production (15%), and for animal feed (10%) [123].

### 3.5. The Significance of Linus Carl Pauling (1901-1994) in Promoting Vitamin C Knowledge Cannot Be Overstated

Linus Pauling was a distinguished figure in the scientific contemporary history, warranting a subsection apart. That said, his well-known biography, which includes two Nobel Prizes (Chemistry in 1954 and Peace in 1962), is not revised here. Nonetheless, when conducting a review as thematically extensive as this one, it is necessary to acknowledge his contribution to promoting vitamin C (Table 1).

Table 1 displays an insightful set of works on vitamin C by Linus Pauling and colleagues. Essentially, his primary focus was on studying the impact of high doses of this vitamin on common cold, flu, and cancer [137]. This paved the way for the rise of an innovative

(orthomolecular) approach to medicine and fresh perspectives for the fight against cancer and its intricate biology (e.g., endothelial dysfunction), despite the criticism of his methodology all along the way [138,139]. The effectiveness of vitamin C as a therapy for cancer continues to be debated [140,141].

**Table 1. Examples of Linus Pauling's Publications on Vitamin C\***

Titles	Year	References
Vitamin C, the common cold and the flu	1970	[124]
Evolution and the need for ascorbic acid	1970	[125]
Vitamin C and the common cold	1971	[126]
The significance of the evidence about ascorbic acid and the common cold	1971	[127]
Are recommended daily allowances for vitamin C adequate?	1974	[128]
Early evidence about vitamin C and the common cold	1974	[129]
Ascorbic acid and cancer: a review	1979	[110]
Effect of dietary ascorbic acid on the incidence of spontaneous mammary tumors in RIII mice	1985	[130]
A proposition: megadoses of vitamin C are valuable in the treatment of cancer	1986	[131]
How to live longer and feel better	1986	[132]
Vitamin C papers	1989	[133]
Respect for vitamin C	1991	[134]
A case history: lysine/ascorbate-related amelioration of angina pectoris	1993	[135]

\*: references [124] and [132] are both books that have topped the best-seller lists [136].

### 3.6. The COVID-19 Pandemic Has Renewed the Interest in Vitamin C

Coronavirus disease 2019 (or COVID-19) is caused by a novel viral agent, SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-2), and was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020, because of its widespread transmission and infection rates [142,143,144,145,146]. A search for COVID-19 and vitamin C on the internet yielded 597 results in 2019 and 11,600 results in 2022. This viral infection has indeed reignited curiosity about the possible therapeutic benefits of vitamin C, despite vaccines being the safe and effective methods of preventing the serious illness.

Vitamin C effectively fulfills the conceptual requirements of a conventional vitamin (subsection 3.4.), still serving as an important bioactive compound, i.e., a compound that can interact with one or more part(s) of living tissues by displaying an immense range of probable effects [147].

As a result, vitamin C may boost immune function in several ways, including: improvement of chemotaxis (or leukocyte migration); neutrophilic phagocytosis and oxidative killing; attenuation of the neutrophil extracellular trap formation (NETosis) and reduction of the uncontrollable inflammatory cytokine production in the alveolar space; differentiation and proliferation of B-

and T-lymphocytes; antibody production; cortisol production; interferon- $\gamma$  production; downregulation of interleukin (IL) -6 and endothelin-1; increased lung epithelial barrier; susceptibility and outcome of low respiratory tract infections [148,149,150,151,152,153,154,155].

The inflammatory response in COVID-19 patients may be dramatic and referred to as cytokine storm because of the large amount of pro-inflammatory molecules released in the plasma (i.e., IL-1b, IL-2, IL-6, IL-8, IL-10, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$  or TNF- $\alpha$ ), potentially leading to acute lung injury, subsequent acute respiratory distress syndrome, multiorgan failure, and death if immediate intensive care unit interventions are not initiated [155,156,157,158].

In addition, obesity is a chronic low-grade inflammatory state and adipose tissue serves as a source of inflammatory mediators (e.g., chemerin (a 163 amino acid protein), galectin-3, resistin, IL-6, TNF- $\alpha$ , leptin, adiponectin, and C-reactive protein) [159,160,161,162]. That is in part why overweight people have a higher risk of COVID-19-related hospitalizations but not death, whereas obese and extremely obese people increase the risk of both hospitalizations and death [163].

The effectiveness of large amounts of vitamin C to treat COVID-19 patients is still being debated.

## 4. Concluding Remarks

Evolution, prehistory, and history are intermingled and consequential events that may be better comprehended when explored together, notably when related to vitamin C, as attempted in the present review article.

Most species can synthesize vitamin C, except for a few, including humans. The recent heated debates on this evolutionary aspect bring to mind the era of the famous English naturalist Charles Robert Darwin (1809-1882), with evolutionists and creationists taking opposing stances and showing, among other aspects, how exciting evolutionary biology is as a scientific field. Today, pseudogenes draw growing attention in multidisciplinary research, especially in cancer biology, but still raise more questions than answers.

The emergence of scurvy as a dreadful clinical repercussion of the inability to synthesize vitamin C has made up a heavy burden to humankind over the centuries, as extensively discussed here. However, only lately have the archeological records revealed the evidence of this terrible disease in the remote past of human beings.

To encourage day-to-day vitamin C consumption and prevent scurvy, health professionals should insistently advocate for the population to consume fresh fruits and vegetables, which are the richest sources of this micronutrient.

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## Conflict of Interest

The author declares no conflict of interest.

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