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The Exogenous Antioxidants

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1. Introduction

One theory that was initially questioned was the proposal of Dr. Denhan Harman (1956) of the University of Nebraska. He was the first researcher to propose Free radicals (FR) as an important cause of cellular aging. Today this theory enjoys wide approval. FR are “disequibrated” molecules that travel through our organism attempting to capture an electron of the stable molecules to obtain its electrochemical stability [1,2].

FR perform many useful functions in the organism (in fact, our own bodies manufacture these in moderate amounts to combat, for example, infections). When the increase of the intracellular contents of FR exceeds the cells’ antioxidant defenses and are not efficient for inhibiting them, this causes organic damage known as Oxidative stress (OS), which leads to a variety of physiological and biochemical changes that induce damage to biological molecules such as nucleic acids, proteins, lipids, etc., which consequently cause deterioration and cell death. An FR comprises any atom or group that possesses one or more unpaired electrons; thus, FR are very reactive[3].

OS traditionally has been considered a static cell-damage process that derives from the aerobic metabolism, and its clinical importance has been recognized to the point of currently being considered a central component of any pathological process. OS in diverse pathological states affects a wide variety of physiological functions, contributing to or providing biofeedback on the development of a great number of human degenerative diseases, such as atherosclerosis, diabetes, cardiomyopathies, chronic inflammatory diseases (rheumatoid arthritis, intestinal inflammatory intestinal disease, and pancreatitis), neurological diseases, high blood pressure, ocular diseases, and pulmonary and hematological disease, cancer, and immunodepression, asthma, among others [4].

This implication does not mean that Reactive oxygen species (ROS) always play a direct role in the development of the disease. In fact, reactive species predispose the organism to diseases caused by other agents. In many cases, oxidative damage is to a greater degree the consequence of the tissue damage that the disease produces than a cause of the disease itself and therefore can contribute to worsening of the tissue damage generated [3].

While our own body produces FR in moderate amounts, amounts that decrease when we age, we must also bear in mind ROS-generated exogenous sources in organisms, such as antibiotics, drugs, alcohol, tobacco, stress, contaminants, chemotherapy, and exposure to Ultra-violet (UV) and ionizing radiation.

On the other hand, numerous epidemiological studies suggest that more persons could avoid the appearance of pathological processes if they consumed antioxidant-rich diets (fruits and vegetables). Thus, it would be possible to protect the organism more efficiently against OS, with the presentation of lesser risk of developing human degenerative diseases.

This has led to conducting experiments to identify the specific components responsible for the positive effects on health by the consumption of foods of plant origin. One explanation that has found great acceptance is that this is due to the presence of antioxidant nutrients such as vitamins C and E, carotenoids, flavonoids, selenium, etc., which would interfere with oxidative damage to the DNA, proteins, and lipids [3].

Antioxidants are synthetic or natural substances that present in low concentrations compared with the biomolecules that they should protect. Antioxidants protect by retarding or inhibiting the harmful effects of FR. They are classified as follows: endogens (glutathione, co-enzyme Q, etc.), which are manufactured by the cell itself; exogens, which enter the organism through the diet (existing in determined foods) or through supplements with antioxidant formulations, and co-factors (copper, zinc, manganese, iron, and selenium). The consumption of antioxidant exogens can increase protection of the body and aid antioxidant endogens in combating diseases [5].

Fortunately, numerous foods and supplements that we ingest are rich in the antioxidants that protect against damage to the cells. Vitamin C, which is found in abundance in citrics and vegetables, is perhaps the best known antioxidant. Vitamin E, which is liposoluble, can be found in nuts, unrefined vegetable oils such as corn, cotton seed, and wheat germ, and in whole grains. Beta carotene, which is converted into vitamin A in the organism, can be found in dark-leafed vegetables, carrots, and sweet potatoes.

In recent years, plant-derived natural antioxidants have been used frequently, given that they present activity that is comparable with the most frequently employed synthetic antioxidants. Antioxidants are also found in a variety of herbs and foods that are to a great extent unknown in and not easily available in our environment, such as green tea, cardo mariano, ginkgo biloba, pine bark, and red wine; however, we do have dulcamara, dragon's blood, cat's claw, anamu/guinea hen weed), garlic, onion, aloe vera, and others that are very rich in antioxidants.

Many benefits are conferred on antioxidants against diverse pathological states; in addition to this, an unequalled richness in natural foods is exhibited as well as our obligation to take advantage of and assess these.

In the present work, the description is performed of the characteristics of the exogenous antioxidants with regard to their employment in human health [6].

2. Vitamins

Vitamins are organic micronutrients that possess no energetic value, are biologically active, and with diverse molecular structure, which are necessary for humans in very small quantities (micronutrients) and which should be supplied by the diet because humans are unable to synthesize and which are essential for maintaining health [7].

The majority of vitamins are not synthesized by the organism, some can be formed in variable amounts in the organism (vitamin D and niacin are synthesized endogenously; the former forms in the skin by exposure to the sun, niacin can be obtained from tryptophan, and vitamins K2, B1, B2, and biotin are synthesized by bacteria). However, this synthesis is generally not sufficient to cover the organism's needs. [8,9].

The functions of the vitamins and the need of the organism for these are highly varied. Persons always need vitamins and at all life stages. However, during specific periods such as growth, pregnancy, lactancy, and disease, the needs are increased [8].

The majority of vitamins have a basic function in the maintenance of health (doing honor to their name: "vita" means life. The term vitamin, proposed for the first time (in 1912) by Polish Chemist Casimir Funk, is demonstrated by the appearance of deficiency or deficiency-related diseases that were caused by the lack of vitamins in the diet; for example, lack of vitamin A can produce blindness and the lack of vitamin D can retard bone growth; vitamins also facilitate the metabolic reactions necessary for utilization of proteins, fats, and carbohydrates.

In addition, today we know that their nutritional role extends beyond that of the prevention of deficiency or deficiency-associated diseases. They can also aid in preventing some of the most prevalent chronic diseases in developed societies. Vitamin C, for example, prevents scurvy and also appears to prevent certain types of cancer. Vitamin E, a potent antioxidant, is a protector factor in cardiovascular disease and folates help in preventing fetal neural tube defects [9].

Traditionally, vitamins have been classified into two large groups in terms of their solubility as follows:

Liposoluble vitamins: A (retinol); D (ergocalciferol); E (tocopherol), and K (filloquinone and menadione), which are soluble in lipids but not in water; thus, they are generally vehiculated in the fat found in foods. These vitamins can accumulate and cause toxicity when ingested in large amounts [9].

These are fat-soluble compounds and are found associated in foods with fats, mainly of animal origin, and are absorbed with them. Therefore, any problem with respect to the absorption of fats will be an obstacle to the absorption of liposoluble vitamins. The latter are stored in moderate amounts in the vital organs, especially in the liver [8].

Hydrosoluble vitamins: The following are vitamins of the B group: [B₁ (thiamin); B₂ (riboflavin); B₃ (niacin); pantothenic acid; B₆ (pyridoxine); biotin; folic acid, and B₁₂ (cyanocobalamin)], and vitamin C (ascorbic acid), contained in the aqueous compartments of foods. [9].

These are water-soluble compounds that are found in foods of animal and plant origin. Different from liposoluble vitamins, water-soluble vitamins are not stored in the body; thus, they should be ingested daily with food to avoid their supply becoming exhausted [8]. The hydrosoluble vitamins participate as co-enzymes in processes linked with the metabolism of organic foods: carbohydrates; lipids, and proteins.

One important difference between these two vitamin groups lies in their final destiny in the organism. An excess of water-soluble vitamins is rapidly excreted in the urine; on the other hand, liposoluble vitamins cannot be eliminated in this manner; they accumulate in tissues and organs. This characteristic is associated with a greater risk of toxicity, which means the ingestion of excessive amounts of liposoluble vitamins, especially vitamins A and E. Vitamin B12 constitutes an exception because it is stored in the liver in important quantities.

2.1. Vitamin C

Vitamin C, also known as ascorbic acid (enantiomer, L-ascorbic acid) is an antioxidant hydrosoluble vitamin, this due to that it is an electron donor, which explains its being a reducer that directly neutralizes or reduces the damage exercised by electronically disequibrated and instable reactive species, denominated Free radicals (FR).

Action: The presence of this vitamin is required for a certain number of metabolic reactions in all animals and plants and is created internally by nearly all organisms, humans comprising a notable exception [10]. Vitamin C is essential for the biosynthesis of collagen proteins, carnitine (which is a pro-catabolic transporter of fatty acids in the mitochondria), neurotransmitters (mediators of cell communications, primarily of nerve expression), neuroendocrine peptides, and in the control of angiogenesis; it aids in the development of teeth and gums, bone, cartilage, iron absorption, the growth and repair of normal connective tissue, the metabolism of fats, and the scarring of wounds; it promotes resistance to infections by means of the immunological activity of the leukocytes [11].

In addition to the biological functions mentioned, there are an infinite number of scientific and pseudoscientific reports that qualify this vitamin as an immunomodulator, an antiviral influenza protector, an antiatherogenic, an antiangiogenic, and as an anti-inflammatory, and debate continues on its activity in cancer and its antioxidant properties, given that there is information that lends support to its procancerigenous and to its role as a pro-oxidant. Currently, this vitamin is the most widely employed vitamin in drugs, premedication, and nutritional supplements worldwide [11]. Various lines of experimental and epidemiological evidence suggest that vitamin C is a powerful antioxidant in biological systems, both *in vitro*

as well as *in vivo*. Health benefits have been attributed to vitamin C, such as the anticarcinogenic, immunoregulator, antiinflammatory, and neuroprotector effect. Vitamin C rapidly eliminates Reactive oxygen species (ROS), Reactive nitrogen species (ROS), or both, and reduces the transitional metallic ions of specific biosynthetic enzymes; thus, it can prevent biological oxidation (García G.A., et al., 2006). The damage exercised by electronically disequibrated and instable Reactive oxygen-derived species (ROS) (Free radicals, FR), nitrogen-derived FR, NOS), and sulfa-derived or mixed FR harm through oxidation any of the cellular macromolecular components. If these are not neutralized, so-called "propagation" or "amplification" is produced and, in the case of oxidation, the peroxides are again oxidized into peroxy radicals [12].

Clinical Uses: Vascular diseases, cancer, cataracts, High blood pressure, acute pancreatitis, the common cold, iron fixation in blood hemoglobin, dermatological uses (photochronaging, photoprotection, prevention of contact dermatitis, non-scarring of wounds, and hyperpigmentation) [9].

Foods are substances or products of any nature that due to their characteristics and components are utilized for human nutrition. Ascorbic acid, commonly known as vitamin C, promotes resistance to infections by means of the immunological activity of leukocytes; it is useful for preventing and curing the common cold, as well as improving iron absorption in the human body and diminishing the incidence of anemia caused by lack of this mineral, which presents a high incidence in Mexican population.

Chemical structure: Ascorbic acid is a 6-carbon ketolactone that has a structural relationship with glucose; it is a white substance, stable in its dry form, but in solution it oxidizes easily, even more so if exposed to heat. An alkaline pH (>7), copper, and iron also accelerate its oxidation. Its chemical structure is reminiscent of that of glucose (in many mammals and plants, this vitamin is synthesized by glucose and galactose).

Vitamin C is found mainly in foods of plant origin and can present in two chemically interchangeable forms: ascorbic acid (the reduced form), and dihydroascorbic acid (the oxidated form) (See Figure 1), with both forms biologically functional and maintaining themselves in physiological equilibrium. If dihydroascorbic acid is hydrated, it is transformed into diketogluconic acid, which is not biologically active, and with this an irreversible transformation. This hydration occurs spontaneously on neutral or alkaline dissolution.

Deficit: It is well known that a deficiency of vitamin C causes scurvy in humans, thus the origin of the name "ascorbic" given to the acid [10]. Scurvy was recognized for the first time in the XV and XVI Centuries as a serious disease contracted by sailors on long sea journeys (it appeared in adults after a nutritional need had existed for >6 months, because sailors had no access to fresh foods, including fruits and vegetables). Prior to the era of research on vitamins, the British Navy established the practice of supplying lemons and other citric fruits to their sailors to avoid scurvy [13]. Scurvy is related with defective collagen synthesis, which manifests itself as the lack of scarring, progressive asthenia, gum inflammation, falling out of the teeth, joint inflammation and pain, capillary fragility, and esquimososis, thus the importance of the ingestion of vitamin C in the diet [11].

Obtaining Vitamin C: This is a nutrient that is localized, above all, in citric fruits and vegetables. All fruits and vegetables contain a certain amount of vitamin C. Foods that tend to be greater sources of vitamin C are, among others, the following: citrics (oranges, limes, lemons, grapefruit); guavas; pineapple; strawberries; kiwis; mangoes; melon; watermelon, and cantaloupe and, as examples of vegetables, green peppers, tomatoes, broccoli, cabbage, cauliflower, green peas, asparagus, parsley, turnips, green tea, and other green-leafed vegetables (spinach), potatoes or sweet potatoes, and yams.

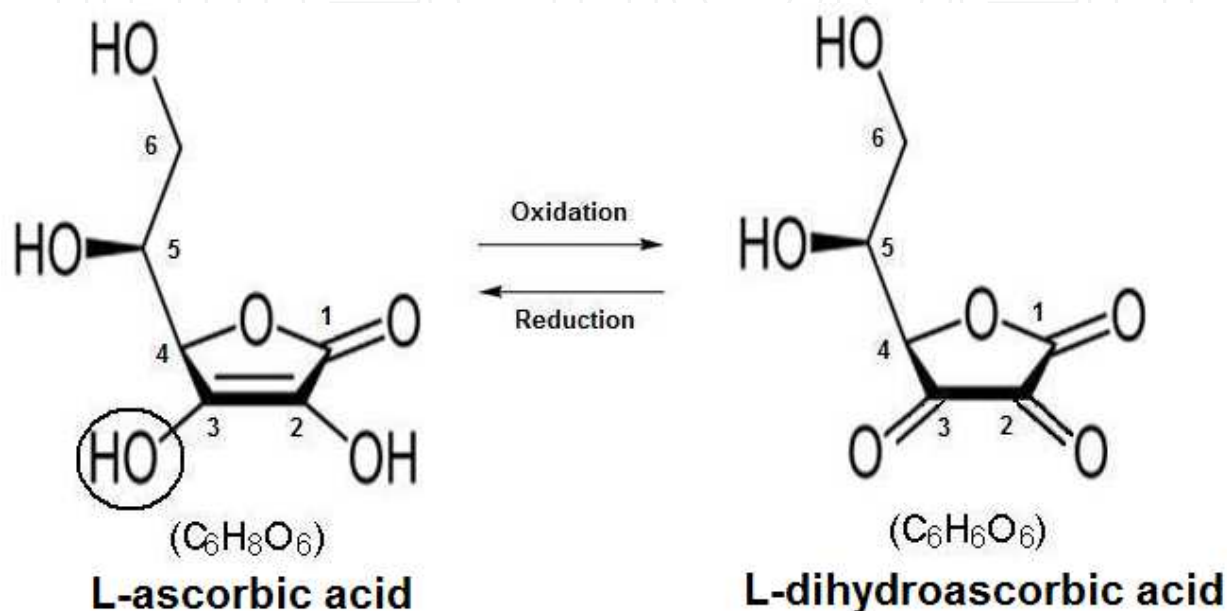


Figure 1. The oxidation-reduction (redox) reaction of vitamin C, molecular forms in equilibrium. L-dihydroascorbic acid also possesses biological activity, due to that in the body it is reduced to form ascorbic acid.

However, it is noteworthy that vitamin C diminishes on boiling, drying, or soaking foods; thus, it is convenient to consume these raw.

Daily recommended doses of ascorbic acid are 75 mg/day (for women) and 90 mg/day (for men). There are between 1.2 and 2 g (20 mg/kg body weight) of ascorbic acid available in the entire organism and its half-life ranges from 10–20 days [11–15].

Absorption: Vitamin C is easily absorbed in the small intestine, more precisely, in the duodenum. It enters the blood by active transport and perhaps also by diffusion. It would appear that the mechanism of absorption is saturable, due to that when large amounts of the vitamin are ingested, the percentage absorbed is much lower (Figure 2). In normal ingestions (30–180 mg), vitamin C is absorbed (bioavailability) at 70–90% vs. a 16% ingestion of 12 g. Its concentrations in plasma are 10–20 mcg/ml.

The vitamin C concentration in the leukocytes is in relation to the concentration of the vitamin in the tissues: therefore, by measuring the concentration of vitamin C in the leukocytes, we can know the real level of the vitamin in the tissues. The pool of vitamin C that humans possess under normal conditions is approximately 1,500 g. When this pool is full, vitamin C

is eliminated at a high percentage by the urine in the form of oxalic acid (catabolite) or, if it is ingested in very high amounts, as ascorbic acid. If there are deficiencies, absorption is very high and there is no elimination by urine. Ascorbic acid is found at high concentrations in various tissues, for example, suprarenal, liver, spleen, and kidneys. Alcohol consumption diminishes absorption of the vitamin, and the smoking habit depletes the levels of the vitamin in the organism; thus, it is recommended that smokers and regular alcohol consumers supplement their diet with vitamin C.

The half-life of ascorbic acid in the organism is approximately 16 days. Thus, the symptoms of scurvy do not appear for months in subjects with a diet deficient in vitamin C [7].

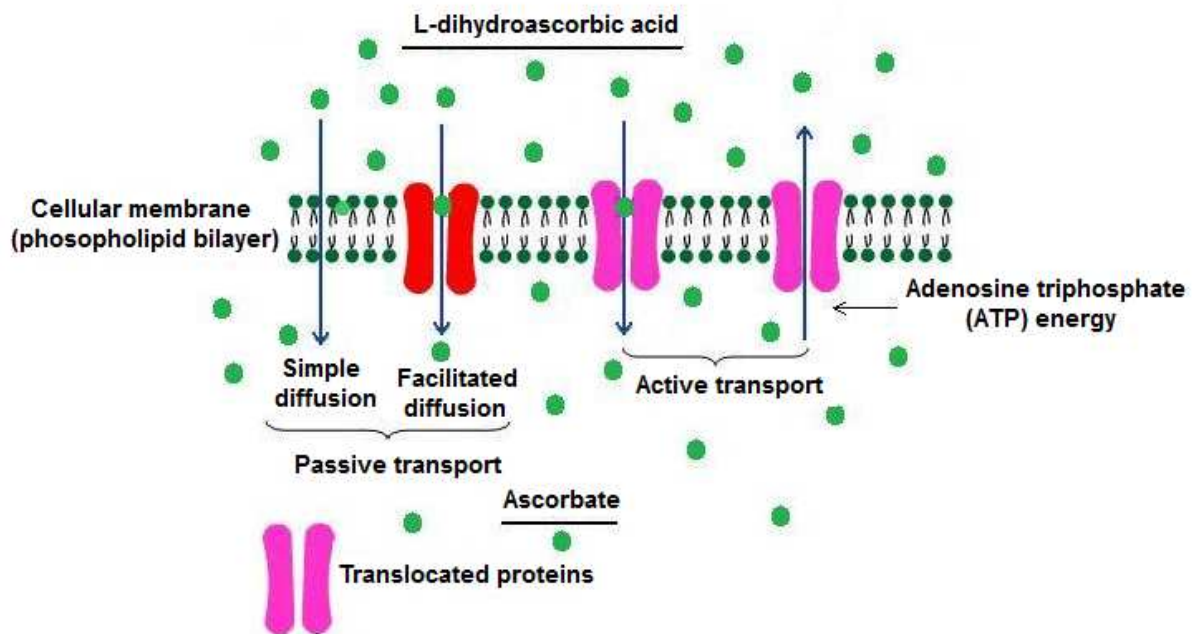


Figure 2. Mechanism of absorption of vitamin C. The L-dihydroascorbic acid molecule is better absorbed than that of L-ascorbic acid. Passive absorption is dependent on a glucose transporter and active absorption is dependent on Na^+ .

Toxicity: It is scarcely probable for vitamin C intoxication (megadose) to occur because it is a hydrosoluble vitamin and excesses are eliminated through the urine. But if the daily dose of vitamin C exceeds 2,000 mg/day, the following can appear [16]:

- Diarrhea
- Smarting on urinating
- Prickling and irritation of the skin
- Important alterations of glucose in persons with diabetes
- Insomnia
- Excessive iron absorption
- Formation of oxalate and uric kidney stones.

Great controversy on the theme of Free radicals (FR) and antioxidants such as vitamin C continues, although there is conceptual dispute on whether these are the cause or consequence of the pathology. Biochemically, L-ascorbic acid donates two of its electrons from a double bond between the carbons in positions 2 and 3 (See Figure 1), and this donation is sequential, because the first molecular species generated after the loss of an electron is an FR denominated ascorbyle acid. Similar to other FR with an unpaired electron, ascorbyle is relatively stable and regularly non-reactive, with half-life of 10–15 seconds.

A great diversity of scientific works has allowed increasing the knowledge of the biological function of vitamin C, but this has also generated doubts, given that controversies have surfaced. One of these controversial points comprises the pro-oxidant activity of vitamin C [12,17]. In the meanwhile, there are starting points, such as that its pro-oxidant activity depends as much on the dose in the diet as on the presence of trace metals, such as iron and free copper, in order for these to produce Fenton-type reactions, and this is amplified by the additional presence of certain FR in the circulating medium [16,18]. This would also depend on the vitamin C-directed reaction.

2.2. Vitamin E

Discovered at the beginning of the 1920s in vegetable oils such as that of wheat germ by Herbert Evans and Katherine Bishop, vitamin E is also denominated tocopherol or the anti-sterile vitamin, due to its activity. Vitamin E is present in small amounts in all of the cells.

Vitamin E is a group of methylated phenolic compounds known as tocopherols and tocotrienols (a combination of the Greek words “τόκος” [birth] and “φέρειν” [possess or carry], which together mean “to carry a pregnancy”). Alpha-tocopherol is the most common of these and biologically that with the greatest vitaminic action. It is a lipophilic antioxidant that is localized in the cell membranes whose absorption and transport are found to be very highly linked with that of lipids. It is considered the most important lipid molecule protector because its action consists of protecting the polyunsaturated fatty acids of cell membrane phospholipids from cellular peroxidation, and also inhibiting the peroxidation of Low-density lipoproteins (LDL). It oxidizes the oxygen singlet, takes up hydroxyl FR, neutralizes peroxides, and captures the superoxide anion in order to convert it into less reactive forms [1].

Fortunately, the foods with the greatest amounts of Polyunsaturated fatty acids (PFA) also tend to have a high content of this vitamin. Sunflower seed oil, one of the foods richest in PFA, also has the highest content of vitamin E among all of the foods that we habitually consume. It is also found in other vegetable oils, in dry fruit, and in eggs. In the mean diet of Spaniards, vegetable oils furnish 79% of the vitamin E that they consume [9].

Ingestion that adequately covers the recommended allowance appears to behave as a factor of protection in cardiovascular disease, on protecting LDL from oxidation, one of the main risk factors of this pathology. Vitamin E acts jointly and synergically with the mineral selenium, another of the organism’s antioxidants.

It can be easily destroyed by the action of heat and of oxygen in the air. Vitamin E is one of the least toxic liposoluble vitamins [9].

Action: It has been proposed that in addition to its antioxidant function, vitamin E can perform a specific physicochemical function in the ordering of the lipic membranes, especially of phospholipids rich in arachidonic acid (thus acting as a membrane stabilizer) [1].

In vivo, vitamin E acts when it breaks the chain of antioxidants, thus preventing the propagation of damage to the biological membranes that give rise to FR, something akin to a protective shield of the cells' membranes that allows them not to age or to deteriorate due to oxygen-containing FR, retarding cellular catabolism, impeding the chain reaction that can produce peroxides from ensuing. It participates in the hemo group and in vitamin E deficiency; hemolytic anemia appears as a result of damage by FR. It also exercises an antitoxic function, a protector in the face of various chemical agents, especially preventing the formation of peroxides from PFA, thus favoring the maintenance and stability of the biological membranes and of the lisosomes in erythrocytes, liver, and muscle [19].

Tocopherols act as intra- and extracellular liposoluble antioxidants within the body. In particular, the tocopherols protect the highly stored fatty acids (PFA) that are present in cellular and subcellular membranes, maintaining the integrity of the biological membranes, as well as other reactive compounds (e.g., vitamins A and C) from the oxidative damage that they could undergo on acting as FR traps. It has also been suggested that the tocopherols play an important role in cell respiration and in DNA and co-enzyme Q biosynthesis.

Tocopherols favor normal growth and development, act as an anticoagulant agent, stimulate the formation of red globules, stimulate the recycling of vitamin C, reduce the risk of the first mortal heart attack in males, protect against prostate cancer, improve immunity, and is a potent antioxidant against cancer in general, cardiac diseases, and FR, thus possessing a potent anti-aging function.

Vitamin E can reduce circulatory problems in the lower limbs, prevent coronary diseases, increase strength and muscular resistance (fostering achievement in sports), drive the sexual metabolism, and relieve menopausal symptoms. It can reduce the formation of scars (stimulating the curing of burns and wounds), could help in the treatment of acne, and is a potential treatment for diaper dermatitis and bee stings.

Chemical structure: The chemical formula for vitamin E ($C_{29}H_{50}O_2$) is utilized for designating a group of eight natural species (vitamers) of tocopherols and tocotrienols (α , β , γ , and δ). Together with vitamins A, D, and K, these constitute the group of liposoluble vitamins, characterized by deriving from the isoprenoid nucleus, soluble in lipids and organic solvents. They are essentials, given that the organism cannot synthesize them; therefore, their contribution is carried out through the diet in small amounts. For efficient absorption by the organism, these require the presence of fatty acids, bile, and lipolytic enzymes of the pancreas and intestinal mucosa [20].

Their structure comprises two primary parts: they contain a substitute aromatic ring denominated chromate and a long side chain (See Figure 3). These eight vitamers are divided

into two basic groups: four tocopherols, and four tocotrienols, which are differentiated in the side-chain saturation; the tocopherols possess a saturated chain, and the tocotrienols, an unsaturated one with three double bonds on carbons 3, 7, and 11 (Figure 4).

Within each group, the vitamers differ in the number and position of the methyl groups in the chromate ring, designating these as α , β , and δ (Figures 4 and 5) [19,20].

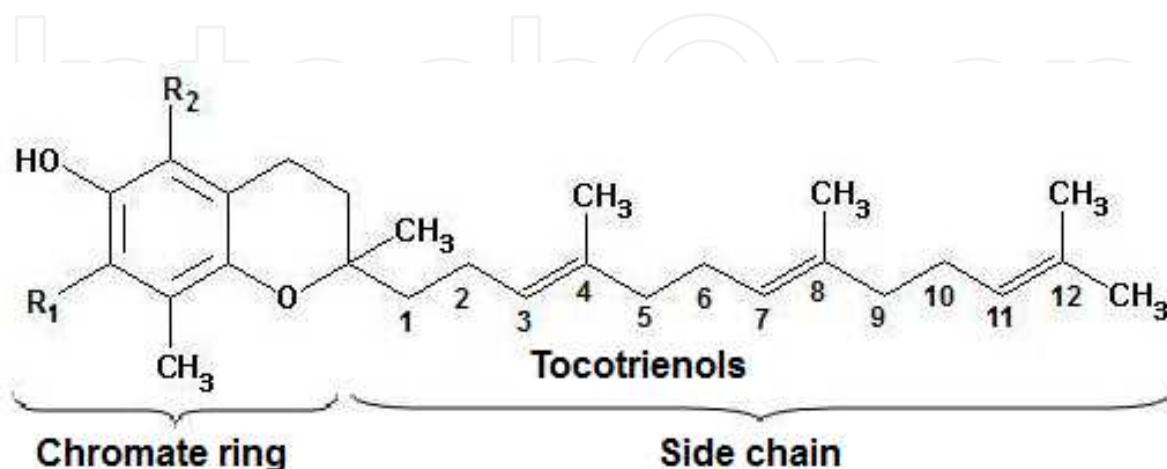


Figure 3. Components of the tocotrienol structure.

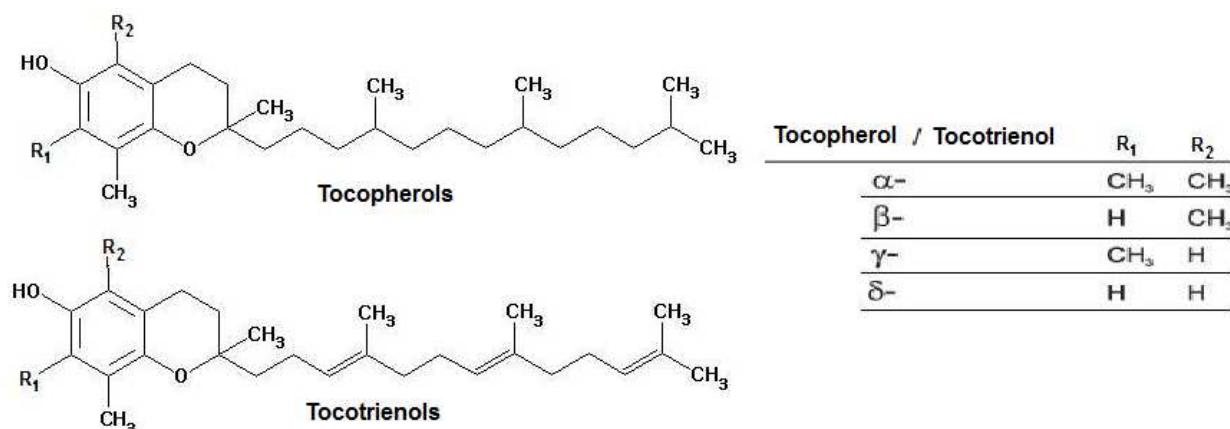


Figure 4. Chemical structure of the possible stereoisomers of the tocopherols and tocotrienols that make up the natural vitamin E. The presence of the -CH₃ or -H groups in the chromate ring define that these substances as α , β , γ , and δ .

The presence of three chiral centers (position C2 of the chromate ring, positions C4 and C8 of the phytyl chain) allow there to be a total of eight configurations depending on the R or S orientation of the methyl group in each of the chiral centers (Figures 3 and 5) [19].

During vitamin E synthesis, equimolar amounts of these isomers (vitamers) are produced.

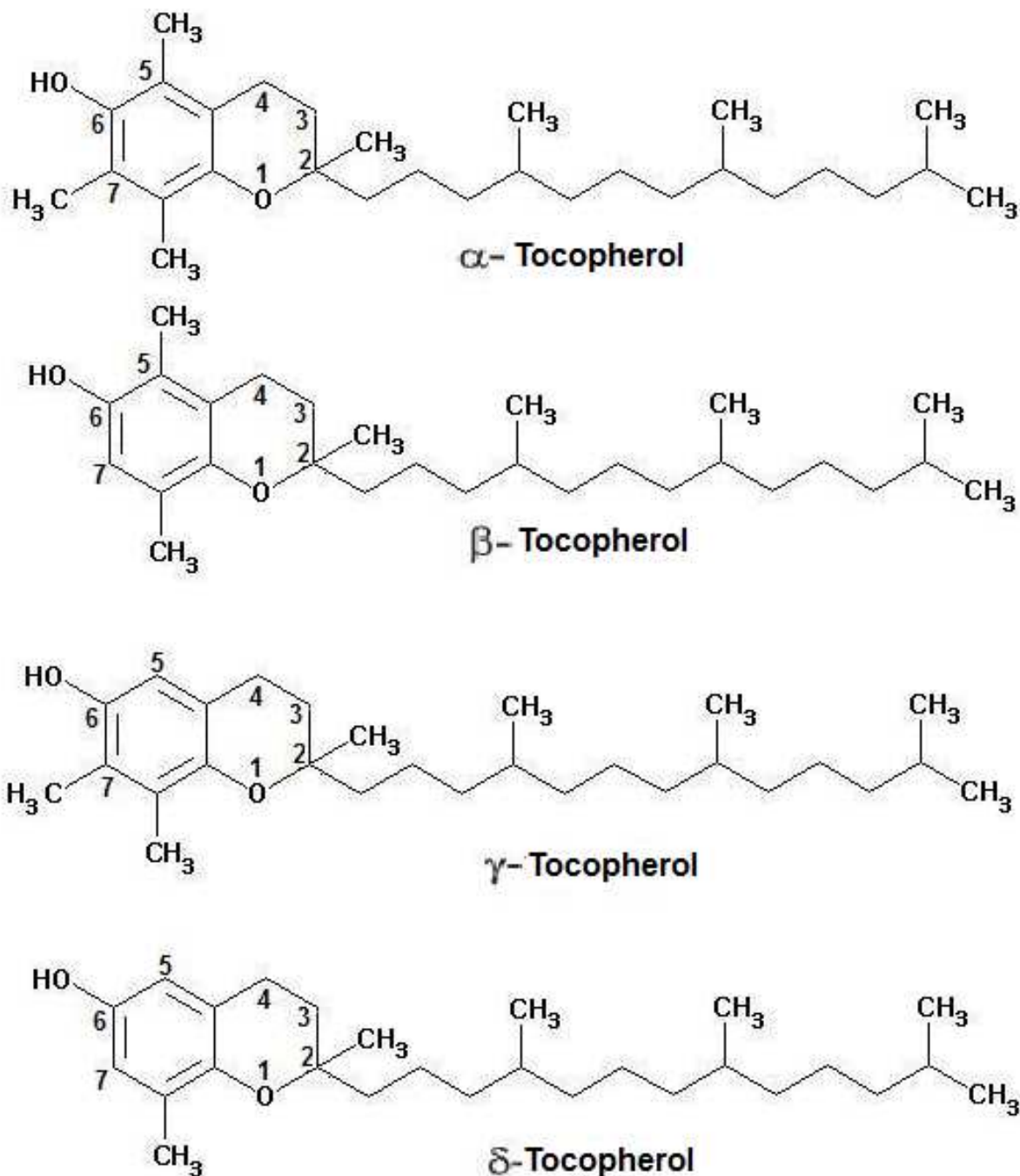


Figure 5. Chemical structure of the tocopherols.

Deficit: The deficiency of vitamin E can be due to two causes: not consuming a certain food that contains it, or poor fat absorption, due to that vitamin E is a liposoluble vitamin, that is, it is diluted in fats for its absorption in the intestine in the micelles.

Vitamin E is essential for humans. Its deficiency is not frequent even with persons who consume diets that are relatively poor in this vitamin, and could develop in cases of intense malabsorption of fats, cystic fibrosis, some forms of chronic liver disease, and congenital

abetalipoproteinemia. The newborn, fundamentally the premature infant, is particularly vulnerable to vitamin E deficiency because of its deficient body reserves. The majority of vitamin E deficiency-associated sequelae are subclinical. Neuropathological alterations have been described in at-risk patients and the most frequent manifestations comprise diverse grades of areflexia, walk proprioception disorders, diminution of vibratory sensations, and ophthalmoplegia [1].

With regard to the relationship of vitamin E deficiency and the development of cardiovascular disease and cancer, there are no conclusive results to date [1,19].

The existence of a lack of vitamin E is rare. If this occurs, it is manifested in specific cases, that is, in the following three situations:

- a. Persons with a difficulty of absorbing or secreting bile or who suffer from fat metabolism-related disease (celiac disease or cystic fibrosis)
- b. Premature infants (with Very low birth weight, VLB) who weigh <1,500 grams at birth
- c. Persons with genetic abnormalities in alpha-tocopherol transporter proteins.

Likewise, vitamin E levels can fall due to a zinc deficiency.

Lipid-absorption disorders can present in adults. From 3 years on, lack of absorption presents neurological conditions. The deficiency appears in less time due to the infants' not possessing so great a vitamin-E reserve.

2.2.1. Symptoms of vitamin E deficiency

Irritability, Fluid retention, Hemolytic anemia (destruction of red globules), Ocular alteration

Damage to the nervous system, Difficulty in maintaining equilibrium, Tiredness, apathy

Inability to concentrate, Alterations in the walk and Diminished immune response.

2.2.2. Vitamin E deficiency-related diseases

Encephalomalacia. This is due to the lack of vitamin E, which does not avoid PFA oxidation of the ration of the vitamin; consequently, hemorrhages and edema are produced in the cerebellum.

Exudative diathesis. This is due to deficient rations of vitamin E and selenium. The disease can be prevented with the administration of selenium, which acts on vitamin E as an agent that favors the storage of selenium in the organism.

Nutritional white muscle or muscular dystrophy. Rations with a scarcity of vitamin E, selenium, and azo-containing amino acids and a high content of polyunsaturated fats cause muscle degeneration in chest and thighs.

Ceroid pigmentation. This corresponds to the yellowish-brown coloration of adipose tissue in the liver due to the oxidation *in vivo* of lipids.

Erythrocytic hemolysis. The FR attack membrane and erythrocyte integrity; thus, these are also hemolysis-sensitive.

This produces sterility in some animals and certain disorders associated with reproduction, death, and fetal reabsorption in females and testicular degeneration in males.

The excess of vitamin E does not appear to produce noxious toxic effects.

Obtaining Vitamin E: Tocopherol-rich dietary sources include the following: alfalfa flour; wheat germ flour (125–100 mg/kg); hen's egg (egg yolk); polished rice (100–75 mg/kg); rice bran; mediator wheat (75–50 mg/kg); dry yeast; dry distillery solubles; barley grains; whole soy flour; corn grains; ground wheat residues (50–25 mg/kg); corn gluten flour; wheat bran; rye grains; sorghum; fish flour; oatmeal; sunflower seed flour; cotton seed flour (25–10 mg/kg); almonds; hazelnuts; sunflower seeds; nuts, and peanuts. Other sources include all vegetable oils and green vegetable harvests, above all those with green leaves, sweet chile peppers, avocado, fresh potatoes, celery, cabbage, fruits, chicken, fish, and butter [19, 20].

1 International unit (IU) of vitamin E = 1 mg alpha-tocopherol, and 1 IU of vitamin E = 0.67 mg of vitamin E. In adults, the Minimum daily requirement (MDR) for vitamin E is 15 mg/day, and up to 200–600 mg/day would not cause any disorder.

The principal sources are vegetable oils and wheat germ. Hydrogenation of the oils does not produce a very important loss of tocopherols in terms of their content in the original oil; thus, margarine and mayonnaise contain this vitamin, in lesser amounts.

One hundred percent of the MDR of vitamin E can be covered with two tablespoons of sunflower seed or corn oil.

Absorption: The absorption of vitamin E in the intestinal lumen depends on the process necessary for the digestion of fats and uptake by the erythrocytes. In order to liberate the free fatty acids from the triglycerides the diet requires pancreatic esterases. Bile acids, monoglycerides, and free fatty acids are important components of mixed micelles. Esterases are required for the hydrolytic unfolding of tocopherol esters, a common form of vitamin E in dietary supplements. Bile acids, necessary for the formation of mixed micelles, are indispensable for the absorption of vitamin E, and its secretion in the lymphatic system is deficient. In patients with biliary obstruction, cholestatic disease of the liver, pancreatitis, or cystic fibrosis, a vitamin E deficiency presents as the result of malabsorption. Vitamin E is transported by means of plasma lipoproteins in an unspecific manner. The greater part of vitamin E present in the body is localized in adipose tissue [19, 20].

The four forms of tocopherol are similarly absorbed in the diet and are transported to the peripheral cells by the kilomicros. After hydrolysis by the lipoprotein lipases, part of the tocopherols is liberated by the kilomicros of the peripheral tissues [19].

Vitamin E accumulates in the liver as the other liposoluble vitamins (A and D) do, but different from these, it also accumulates in muscle and adipose tissue.

Toxicity: High doses of vitamin E can interfere with the action of vitamin K and also interfere with the effect of anticoagulants: hemorrhages.

Since 2001, it was calculated that 70% of the U.S. population occasionally consumes dietary supplements and that 40% do so on a regular basis. In 2002, Montuiler and collaborators informed, in a population of physicians, that 64% consumed doses of >400 IU/day of vitamin E and that the average obtained from food sources is 9.3 mg of α -tocopherol per day (approximately 14 IU/day). In 2005, Ford and coworkers found that 11.3% of the U.S. population consumes at least 400 IU/day of vitamin E and that median daily ingestion is 8.8 IU/day.

Part of the potential danger of consuming high doses of vitamin E could be attributed to its effect on displacing other soluble antioxidants in fats and breaking up the natural balance of the antioxidant system. This can also inhibit the Glutathione S-transferase (GST) cytosolic enzymes, which contribute to the detoxification of drugs and endogenous toxins. In fact, one study on α -tocopherol and β -carotene demonstrated a significant increase in the risk of hemorrhagic shock among study participants treated with vitamin E. Other data suggest that vitamin E could also affect the conversion of β -carotene into vitamin E and the distribution of the latter in animal tissues. Vitamin E possesses anticoagulant properties, possibly on interfering with the mechanisms mediated by vitamin K. In recent studies conducted *in vitro*, it was demonstrated that vitamin E potentiates the antiplatelet effects of acetylsalicylic acid; therefore, one should be alert to this effect when both substances are consumed [19].

2.3. Vitamin A

This is a term that is employed to describe a family of liposoluble compounds that are essential in the diet and that have a structural relationship and share their biological activity. It is an antioxidant vitamin that eliminates Free radicals (FR) and protects the DNA from their mutagenic action, thus continuing to halt cellular aging. Their oxygen sensitivity is due to the large amount of double loops present in their structure. Their biological activity is attributed to all-*trans* retinol, but from the nutritional viewpoint, they should be included in under the denomination of A provitamins, certain carotenoids, and similar compounds, the carotenals, which have the capacity to give rise to retinol from the organism.

Vitamin A is a hydrosoluble alcohol that is soluble in fats and organic solvents. It is stable when exposed to heat and light, but is destroyed by oxidation; thus, cooking in contact with the air can diminish the vitamin A content in foods. Its bioavailability increases with the presence of vitamin E and other antioxidants [21].

Function: In its different forms, vitamin A, also known as an antixerophthalmic, is necessary in vision, normal growth (its deficiency causes bone growth delay), reproduction, cellular proliferation, differentiation (which confers upon it a role in processes such as spermatogenesis, fetal development, immunological response, etc.), fetal development, and the integrity of the immune system. Others of these include its being an antioxidant, amino acid metabolism, the structure and function of other cells, reproduction, and epithelial tissues.

Vitamin A participates in the synthesis of glycoproteins, which contributes to maintaining the integrity of epithelial tissue in all of the body's cavities. Epithelial dissection especially affects the conjunctivae of the eye (xerophthalmia), which renders the cornea opaque and causes crevices, producing blindness and facilitating eye infections.

Sources: Retinol is only found in the lipidic part of foods of animal origin as follows; whole milk; lard; cream; cheese; egg yolk; eels, and fatty fish, due to their self-storage in the liver and in the oils extracted from the liver. The latter, as well as the oils extracted from the liver (veal and pork), comprise an important source of vitamin A. Cod liver oil constitutes source richest in vitamin A, although this cannot be considered a food in the strictest sense. In the case of skim/low-fat milk, this vitamin would be eliminated, but by law it is restituted to its original content; examples of these include manchego cheese, margarine, and butter.

Vegetables contain only provitamins or carotenes (all of these coloring pigments, such as alpha, beta, and gamma carotene). Garden vegetables (spinach and similar vegetables), carrots, sweet chile peppers, potatoes, tomatoes, and red and yellow fruits are the main suppliers. We must bear on mind that there are numerous carotenes that do not possess any provitaminic A activity, such as lycopene from the tomato, although it does act as a neutralizer of FR [21, 22].

Structure of Vitamin A: This vitamin is a diterpene ($C_{20}H_{32}$) that can present in the following various molecular forms:

Retinol (See Figure 6), when the side chain terminal is an alcohol group ($-CH_2OH$)

Retinal, the carbon terminal, is an aldehyde ($-CHO$)

Retinoic acid, when the terminal group is acidic ($-COOH$)

Retinyl-palmitate, in the case of lengthening of a side chain from esterification with palmitic acid ($-CH_2O-CO-(CH_2)_{14}-CH_3$).

Absorption: The metabolism of the vitamin responds to the same general mechanisms of digestion and absorption as those of other lipidic substances. Absorption is carried out in the form of carotenes or similar substances at the intestinal level within the interior of the micelles and quilomicrons, together with other fats.

Retinol esters are absorbed from 80–90%, while the beta-carotenes are absorbed at only 40–50%. Factors in the diet that affect carotene absorption include the origin and the concentration of the fat in the diet, the amount of carotenoids, and the digestibility of the foods. Vitamin A is first processed in the intestine, and afterward it arrives at the liver via portal, the liver being the main storage organ. In addition, the liver is responsible for regulating the secretion of the retinol bound to the retinoid-binding protein. Carotene absorption in particular is very inefficient in raw foods, and its content in lipids in the diet is low. The efficiency of conversion into retinol, which is quite variable and, in general, low, depends not only on the structure of the carotenoids, but also on their proteinic ingestion. Thus, when carotene ingestion is very high, those which have not been transformed into retinol in the retinal mucosa are absorbed unaltered, bind with the lipoproteins, and are deposited in the skin and the mucosa, on which they confer a typical yellowish color, constituting hypercarotenosis [21].

Toxicity: Both the deficiency as well as the excess of vitamin A causes fetal malformations. Ingestion of large amounts of this vitamin can give rise to skin alterations (scaling), hair fall, weakness, choking, vomiting, etc. In extreme cases, great amounts accumulate in the liver, producing hepatic disorders that end up as fatty liver.

It is noteworthy that the administration of vitamin A in chronic form and at doses higher than the recommended doses those can produce a clinical condition of toxicity characterized by fatigue, irritability, cephalaea, febricula, hemorrhages in different tissues, and cutaneous alterations.

In children, this can trigger the early closing of the long bones, which causes the height to descend. Megadoses of vitamin A can produce acute intoxication that will be characterized by clinical features of sedation, dizziness, nausea, vomiting, erythema, pruritis, and generalized desquamation of the skin. We should also point out that in the elderly, the safety margin when we administer this vitamin is small; thus, we must be especially cautious and adjust the dose well [21].

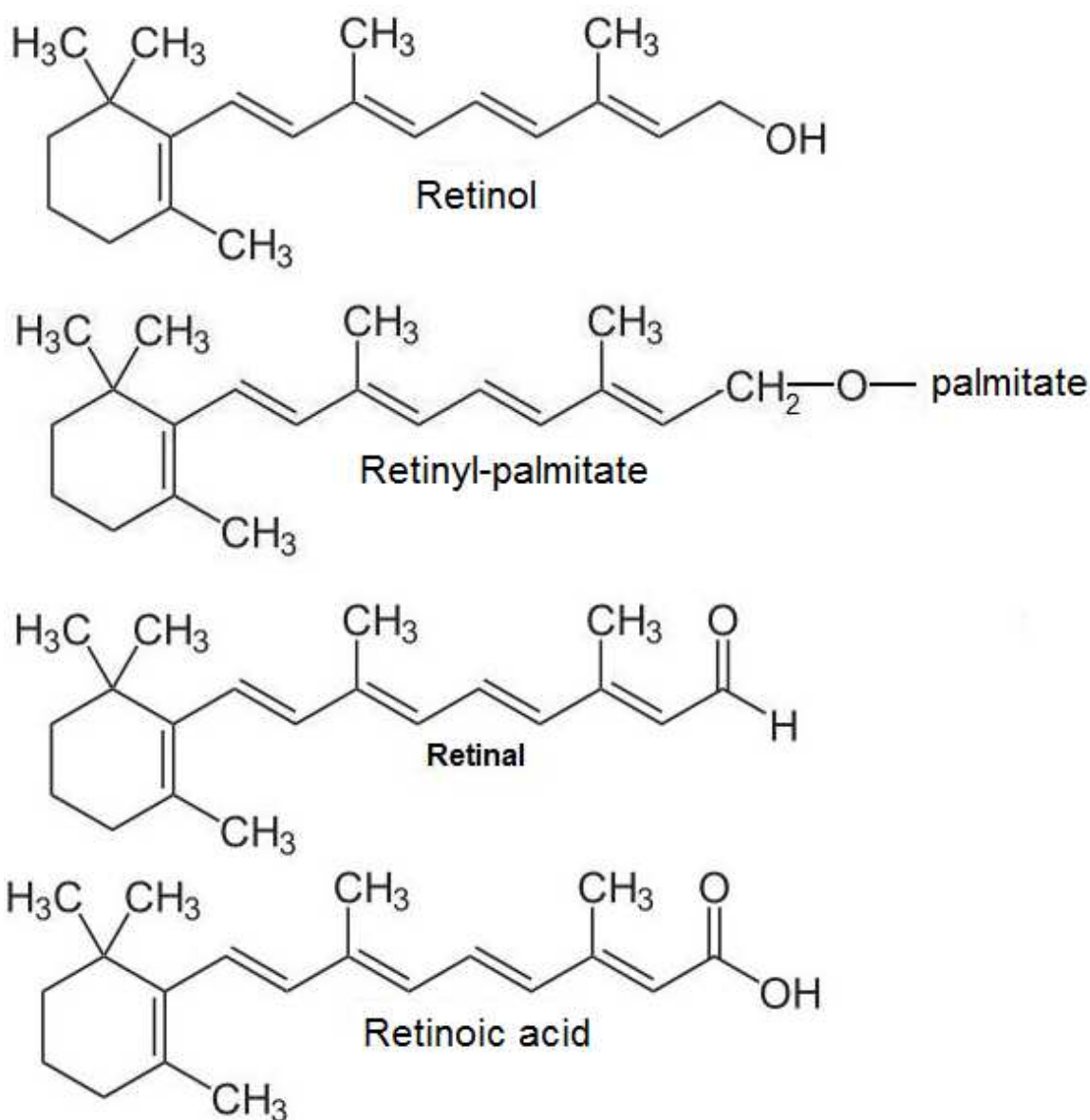


Figure 6. Molecular forms of vitamin A.

2.4. Flavonoids and their antioxidant actions

Flavo comes from the Latin *flavus* and means the color found between yellow and red, such as that of honey or of gold, and flavonoid refers to an aromatic group, with heterocyclic pigments that contain oxygen, which are widely distributed among plants, constituting the majority of yellow, red, and blue fruits. Consequently, flavonoids are found in abundance in grapes, apples, onions, cherries, and cabbage, in addition to forming part of the ginkgo biloba tree and *Camellia sinensis* (green tea). On consuming these, we obtain the anti-inflammatory, antimicrobial, antithrombotic, antiallergic, antitumor, anticancerigenous, and antioxidant properties. With regard to the latter properties, these lie within its function in the nervous system, because a protector relationship has been observed with regard to neurodegenerative diseases [22].

Flavonoids are Low-molecular-weight (LMW) compounds that share a common skeleton with diphenylpyrenes (C6-C3-C6); a flavonoid is a 2-phenyl-ring (A and B) compound linked through the pyrene C ring (heterocyclic). The carbon atoms in the C and A rings are numbered from 2–8, while those of the B ring are numbered from 2'–6'12 (Figure 7). The activity of flavonoids as antioxidants depends on the redox properties of their hydroxy phenolic groups and on the structural relationship among the different parts of their chemical structure[22].

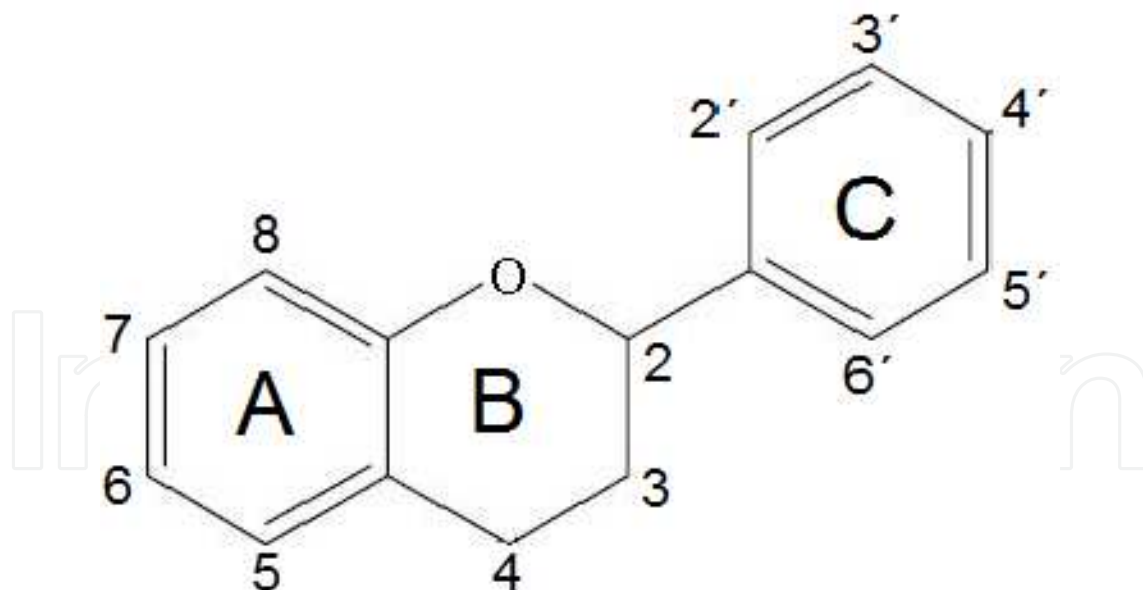


Figure 7. Base structure of the flavonoids

Thanks to the variations of pyrene, the flavonoids achieved classification, as shown in Table 1 (Antiatherogenic properties of flavonoids: Implications for cardiovascular health, 2010) [24].

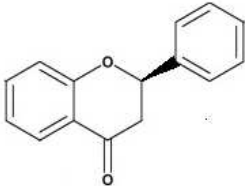
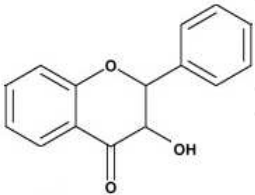
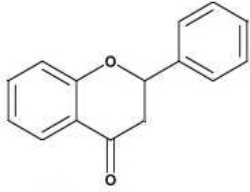
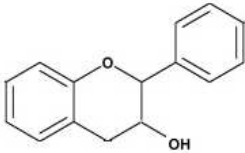
Name	Structure	Description	Family members	Dietary sources
Flavanones		Carbonyl group at position 4 and an -OH group in position 3 of ring C	Quercetin, myricetin, isorhamnetin, kaempferol, pachypodol, rhamnazin	Onions, apples, broccoli, cranberries, berries, grapes, parsley, spinach
Flavan-3-ols		With an -OH group in position 3 of ring C	Catechins, epigallocatechin gallate, epicatechins, epicatechin gallate	Tea, red wine, cocoa, grapes, plums, fruits, legumes
Flavones		Have a carbonyl group in position 4 of ring C and lacking the hydroxyl group at position C3	Apigenin, nobiletin, tangeritin, luteolin	Celery, lettuce, parsley, citrus fruits, beets, bell peppers, spinach, Brussels sprouts, thyme
Anthocyanidins		Carbonyl group at position 4 and an -OH group in position 3 of ring C	Cyanidin, delphinidin, peonidin, malvidin, pelargonidin	Red wine, blueberries, cranberries, black currants, plums, red onions, red potatoes

Table 1. Classification of flavonoids

Distribution: The flavonoids are widely distributed among the higher plants, with the rutaceous, polygonaceous, compound, and umbelliferous plant families the principal ones containing flavonoids. Flavonoids abound, above all, in young, aerial plant parts and in those most exposed to the sun, such as the leaves, fruits, and flowers, because solar light favors their synthesis, controlling the levels of the auxins (vegetable hormones), which are growth regulators.

These compounds are important for the plant, similar to what occurs with the greater part of secondary metabolites, in addition to being responsible for the coloration of many flowers, fruits, leaves, and seeds, achieving >5,000 distinct flavonoids, because these can be found in the following groups:

- a. Eliciac acid: found in fruits such as grapes and in vegetables
- b. Anthocyanidines: the pigment responsible for the reddish-blue and red color of cherries
- c. Catechins: found in black and green tea
- d. Citroflavonoids: such as quercetin, lemonene, pyridine, rutin, and orangene. The bitter flavor of the orange, lemon, and grapefruit confers orangene on these fruits, while lemonene has been isolated from the lime and the lemon.

- e. Isoflavonoids: such as genestein and daidzein, present in soy foods such as tofu, soy milk, soybeans, soy vegetable protein, tempeh/fermented soybeans, miso/soybean paste, and soy flour
- f. Kaempferol: found in broccoli, leeks, endives, red beets, and radishes
- g. Proanthocyanidines: these appear in grape seeds, sea pine bark extract, and in red wine.

These merit incorporation into the group of essential nutrients. The mean value of the ingestion of flavonoids is 23 mg/day. The main flavonoid consumed is quercetin, tea being its main source [22].

Properties: The flavonoids are white or yellowish solid, crystallized substances. Their hemiterosides are soluble in hot water, alcohol, and polar organic solvents, being insoluble in apolar organic solvents. However, when they are in their free state, they are scarcely hydro-soluble, but are soluble in more or less oxygenated organic substances, depending on their polarity.

On the other hand, these are easily oxidizable substances; thus, they exert an antioxidant effect because they are oxidized more rapidly than other types of substances [23].

Pharmacological activity: Pharmacologically, flavonoids are prominent due to their low toxicity, presenting in general activity on the vascular system with P vitaminic action (protector effect of the vascular wall due to the diminution of permeability and to the increase of capillary resistance). Likewise, they possess an antioxidant effect, can inhibit lipid peroxidation, have antimutagenic effects, and possess the capacity to inhibit diverse enzymes [23, 24].

Antioxidant functions: The flavonoids' antioxidant action depends mainly on their sequestering capacity of FR and on their chelant properties of metals such as iron, impeding the catalytic actions of FR, and they also act by inhibiting the enzyme systems related with vascular functionality, such as the following: Catechol-O-methyl transferase (COMT), with which it increases the duration of the action of the catecholamines, thus inciding in vascular resistance; histidine decarboxylase, thus affecting the histamine's action, and the phosphodiesterases, thus inhibiting platelet aggregation and adhesiveness, in addition to the following oxidases: lipo-oxygenase; cyclo-oxygenase; myeloperoxidase, and xanthine oxidase, therefore avoiding the formation of Reactive oxygen species (ROS) and organic hydroperoxides.

In addition to this, it has been observed that they also indirectly inhibit oxidative processes, such as phospholipase A₂, at the same time stimulating others with recognized antioxidant properties, such as catalase and SOD.

With respect to their structure, flavonoids are their hydroxylic constituents in positions 3' and 4'; in the B ring, they demonstrate more action as antioxidants and this effect is potentiated by the presence of a double bond between carbons 2 and 3 and a free OH group in position 4. Additionally, the glycols show to be the most potent in their antilipoperoxidative actions than in their corresponding glycosidic actions.

As previously mentioned, quercetin is the flavonoid that unites the requisites for exercising an effective antioxidant function, because it is five times higher than vitamins A and C and additionally possesses a hydrosolubility similar to that of the latter. Therefore, rutin (quercetin-3-*b*-D-rutinoside) is, to date, the sole flavonoid with a pharmacological presence in Mexico.

There is a synergic effect with all of the vitamins to which we have alluded. This is due to that ascorbic acid reduces the oxidation of quercetin in such a way that combines with it and allows the flavonoids to maintain their functions for a longer time. For its part, quercetin protects vitamin E from oxidation.

The flavonoids remove reactive oxygen, especially in the form of SOD, hydroxyl radicals, hydroperoxides, and lipid peroxides, blocking the harmful effects of these substances on the cell, in which antioxidant protection of flavonoids has been corroborated in the following: queratinocytes; dermal fibroblasts; sensory lymph nodes; the endothelium; nervous tissue, and LDL.

On the other hand, the flavonoids exercise other actions as follows: diuretic; antispasmodic; anti-gastriculcerous, and anti-inflammatory.

In phytotherapy, the flavonoids are mainly employed in cases of capillary fragility as venotonics, although they are also utilized in proctology, metrorrhages, and retinopathies [22].

2.5. Pro-oxidant mechanisms

Due to the structural characteristics of some flavonoids, such as the anthocyanidines, these cause low oxidation potentials ($EP/2$), which permits them to reduce Fe^{3+} and Cu^{2+} in order for them to undergo auto-oxidation or even to become involved in the redox recycling process, acting in this manner as pro-oxidant agents, which explains the mutagenic and genotoxic effects of some flavonoids.

Some of these mechanisms include the temporary reduction of Cu (II) to CU (I), auto-oxidation of the aroxyl radical and generating the superoxide anion (O_2^-) that, on following its general sequence, becomes the harmful hydroxyl radical (HO.), as well as the affectation of the functions of the components of the nuclear antioxidant defense system: glutathione, and glutathione-S-transferase.

What determines the antioxidant or pro-oxidant character is the redox stability/lability of the radical compound forming part of the original flavonoid. The pro-oxidant actions only appear to be produced when the flavonoid doses are excessively high [25].

Under this heading, we will present a brief review of the remaining antioxidants present in our diet, their activity, and the foods that supply them.

2.6. Lycopene

Lycopene is the carotenoid that imparts the red color to the tomato and watermelon and that it not converted into vitamin A in the human organism, which does not impede it from possessing very high antioxidant properties.

The highest concentrations of lycopene are found in prostatic tissue. High consumption of lycopene has been related with the prevention of some cancer types, precisely that of the prostate.

Although the tomato is the greatest source of lycopene, there are also other vegetables and fruits that present intense colors, such as watermelons, papayas, apricots, and pink grapefruit. The tomato is the food that concentrates the greatest amount of lycopene, and it should be considered that there are factors that affect its assimilation into the organism, such as its maturity, the distinct varieties, or the manner of cooking, all of which exert an influence on the amount and degree of exploitation of lycopene.

Of all of these, the fried tomato is that which best assimilates this substance, frying being the best way of cooking because, in addition to the heat, there is a certain amount of fat involved, which renders better assimilation of lycopene (fat-soluble). In concrete fashion, its presence in the fried tomato is some 25 μg per 100 g, while in the fresh tomato, this is around 2 μg per 100 g [6, 26, 27].

3. Minerals

Other potent antioxidants include minerals such as copper, manganese, selenium, zinc, and iron. These minerals exercise their antioxidant function in diverse processes and metabolic steps in the organism [6, 26, 27].

3.1. Zinc

Zinc intervenes in >200 enzymatic reactions and its deficit increases the production of oxidant species and Oxidative stress (OS) [6, 26, 27].

3.2. Copper

Copper participates in functions with antioxidant features of the enzyme family denominated Superoxide dismutase (SOD), which is responsible for eliminating the superoxide anion.

It empowers the immune system, participates in the formation of enzymes, proteins, and brain neurotransmitters (cell renovation and stimulation of the nervous system) and is an anti-inflammatory and anti-infectious agent.

Similarly, it facilitates the synthesis of collagen and elastin (necessary constituents of the good state of the blood vessels, lungs, and the skin).

In addition, it acts as an antioxidant, protecting the cells from the toxic effects of FR, and it facilitates calcium and phosphorous fixation [6, 26, 27].

3.3. Manganese

Manganese also intervenes in this family of enzymes, concretely, in enzymes localized within the mitochondria [6, 26, 27].

3.4. Selenium

Selenium intervenes in the synthesis of enzymes related with the oxidative function, such as glutathione peroxidase, which, as its name indicates, eliminates peroxide groups, including oxygen peroxide.

This mineral is incorporated into proteins in the form of selenoproteins and, in this manner, aids in the prevention of cell damage. Epidemiological studies related the lack of selenium in the diet with the incidence of lung, colorectal, and prostate cancer.

The selenium content in the diet is directly related with the selenium content of the soil in which the food was grown. Thus, selenium-deficient soils give rise to a deficit of this element in the population, as in the case of China.

In this specific latter case, the method-of-choice comprises supplementing the diet with contributions of selenium, preferably in the form of selenomethionide, which is the analog, organic form of selenium and which easily increases selenium levels in the blood [6, 26, 27].

3.5. Iron

Iron forms part of the organism's antioxidant system because it contributes to eliminating the peroxide groups. However, its capacity to change valence with ease (2+/3+) renders that it can also intervene, depending on the environment, in the formation of Free radicals (FR) [6, 26, 27].

3.6. Co-enzyme Q

Co-enzyme Q10 or ubiquinone is a liposoluble compound that can be carried in many foods, although it can also be synthesized in the human organism. Co-enzyme Q10 diminishes with age; thus, the metabolic processes in which it has been found implicated are also co-enzyme Q10-sensitive.

Given its liposolubility, its absorption is very low, especially when the diet is poor in fats.

Its principal antioxidant activity resides in that, in its reduced form, it is a liposoluble antioxidant that inhibits lipid peroxidation in LDL. It is also found in the mitochondria, where it could protect protein membranes and the DNA from the oxidative damage that accompanies lipid peroxidation in these membranes.

It additionally acts as an immune system stimulant and through this stimulation also functions as an anticancerigen. In addition, it is capable of directly regenerating alpha-tocopherol [6, 26, 27].

4. Lipoic acid

Lipoic acid or thioctic acid is also a compound that forms part of the antioxidant capital of the organism.

Numerous studies have shown the protector effect of red globules and of the fatty acids of oxidative damage typical of intense exercise and excessive exposure to the sun's UV rays.

It is synthesized by plants and animals, as well as by the human organism, although in the latter case, in very small amounts. Lipoic acid is considered a very good regenerator of potent antioxidants such as vitamin C, vitamin E, glycation, and co-enzyme Q10. It is liposoluble and hydrosoluble, which means that it can act on any part of the organism.

It is found in spinach and similar green-leafed vegetables, broccoli, meat, yeast, and in certain organs (such as kidney and heart) [6, 26, 27].

4.1. Naringenine

The hypolipidemic and anti-inflammatory activities *in vivo* as well as *in vitro* of the flavonoids of citric fruits have been widely demonstrated. Among the flavonoids, naringenine, one of the compounds that causes the bitter taste of grapefruit, has been studied extensively in recent years. In a recently conducted clinical assay, it was found that naringenine reduced Low-density-lipoprotein (LDL) levels in the circulation of 17% of patients with hypercholesterolemia. Additionally, the reducer effects of cholesterol in rabbits and rats were demonstrated, in addition to the reducer effects of Very-low-density-lipoprotein (VLDL) levels through the inhibition of key proteins for their assembly. Other studies reported that naringenine activates enzymes that are important for the oxidation of fatty acids, such as CYP4A1 [28].

5. Conclusion

A good diet influences the development and treatment of diseases, it is increasingly evident. After that epidemiological studies have shown the association between moderate consumption of certain foods and reduced incidence of various diseases at the rate of these observations has attracted considerable interest in studying the properties of substances inherent in the chemical composition of food. Among the characteristics of these substances is the antioxidant activity, associated with the elimination of free radicals and therefore to the prevention of early stages which can trigger degenerative diseases. In this regard it is important to continue the study of dietary antioxidants on the activity may have on human diseases, paying attention to the substances primarily natural antioxidants of food and synthetic way to assess its protective effect on the body.

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