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Review Article

A New Approach on Carotenoids: Classification; Bioavailability and Further Industrial Applications

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Abstract

Carotenoids are versatile isoprenoids that have been related to a number of health benefits. Their presence in foods, dietary intake and circulating levels have been associated with a reduced incidence of obesity, diabetes, certain types of cancer, and even lower total mortality. In this review, several considerations for their safe and sustainable use in foods mostly intended for health promotion are provided. Specifically, information about biosynthesis, sources, ingestion, and factors affecting their bioavailability is summarized. Furthermore, their health-promoting actions and their importance in public health regarding their contribution to reduce the risk of several deseases are synthesized. Also, in this review is emphasized carotenoids benefits as potential strategy for nutraceuticals, pharmaceutical and cosmetic industrial applications.This study also addressed the significant obstacles as well as the synergistic factors that interfere with the bioavailability and consequent biological functions of carotenoids. Finally, this review enhances the use of carotenoids as functional compounds in different industries.

Keywords: Natural Pigments; Chemical Strutures; Functional Properties; Bioavailability; Carotenoids Applications

Introduction

Carotenoids are a group of pigments present mostly in the plant kingdom. They are responsible for yellow, orange, and red colors in plants, and are commercially used as natural colorants and ingredients in supplements [1]. In fact, the color expression of natural pigments has a significant influence on consumer choice [2]. According to some studies, there are three main categories of factors that consumers find relevant concerning the visual appearance of foods: color, shape and physical form/damage, respectivelly [3-5]. The occurrence of carotenoids in nature is hug and they can be found in several different living beings, from microorganisms to animals. These pigments can be synthesized by plants and some bacteria, fungi, algae, but not in animals. Since animals do not synthesize these pigments, they are accumulated in their bodies such as crustaceans (shrimp, lobster, crab), birds (flamingo), and fish (trout and salmon) [6].

In recent years, studies of plant pigments have increased in importance, given their provitamin A activity, and they have been classified as natural antioxidants. Several studies have shown evidences of their role in nutrition and human health. Usually they are related with the prevention of chronic degenerative diseases, cardiovascular diseases, cancer, macular degeneration and cataract [7-9]. Also, carotenoids are involved in immune system modulation and cell communication, embryonic development, hematopoiesis and; apoptosis, and possess antioxidant, anti-inflammatory, anti-angiogenic and antiproliferative properties [10,11].

This work summarizes the main results achieved in improving the bioaccessibility and bioavailability of carotenoids, considering their chemical structures, nutritional or nutraceutical value, and, as a result, their importance for human health. The nutritional (food and feed), health, of these colored compounds provide profitable benefits, which will be increased due to food and beverage supplementation, intensive aquiculture as substitute for fishery depletion, and health properties. Carotenoid discovery, research and development has a long story, which is as highly active and industrially attractive now more than ever.

Carotenoids

Structure and classification

Carotenoids are a class of fat-soluble pigments, tetraterpenes (C40) composed of isoprene units, isopentenyl pyrophosphate (IPP), and its isomer dimethylallyl diphosphate (DMAPP), both of which contain five carbon atoms (C5) [2]. Depending on the producing organism, these molecules can be obtained via mevalonic acid (MVA) or methylerythritol phosphate (MEP). Acetyl-CoA is used in the first route to produce IPP. In the second step, IPP and DMAPP are synthesized from pyruvate and glyceraldehyde-3-phosphate. Carotenoid biosynthesis in plants follows the MEP pathway, which produces IPP and DMAPP after a series of reactions. The condensation of these two isoprenes produces the geranyl diphosphate molecule (C10), which after two condensation reactions with two molecules of IPP yields the geranyl geranyl diphosphate (GGPP). This is a precursor to the phytoene molecule (C40), without chromophore action, but the first carotenoid formed by the condensation of two GGPP molecules (C20) [12]. In fact, the synthesis of phytoene catalyzed by phytoene synthase (PSY) is the most regulated step of the pathway. The biosynthesis of carotenoids carry on with several desaturations (z-carotene desaturase (ZDS), phytoene desaturase (PDS), isomerizations (z-isomerase (Z-ISO) and carotenoid isomerase (CRTiso)), and cyclations (lycopene β-cyclase (LCYB) and lycopene ε-cyclase (LCYE) to produce diverse colored carotenoids including lycopene and α- and β-carotene [13]. Also, light is na important cue that stimulates both plastid development and biosynthesis of carotenoids in plants. Figure 1 represent the simplified route of carotenoid synthesis.

Figure 1: Simplified carotenoid synthesis pathway. Abbreviations of enzymes: phytoene synthase (PSY), phytoene desaturase (PDS), z-carotene desaturase (ZDS), z-isomerase (Z-ISSO), carotenoid isomerase (CRTiso), lycopene β-cyclase (LCYB), licopene ε-cyclase (LCYE), carotene β-hydroxylase (CHYB), carotene ε-hydroxylase (CHYE), violaxanthin de-epoxidase (VDE), zeaxanthin epoxidase (ZEP).

In addition to molecules with 40 atoms of carbon, it is possible to find carotenoids with longer or shorter carbon chains. The occurrence of carotenoids with 45 or 50 carbon atoms is due to the addition of a or two molecules of isoprene to the backbone hydrocarbons, as is the case with decaprenoxanthin carotenoid. Carotenoids with fewer than 40 carbon atoms are classified as apocarotenoids or norcarotenoids. The first group is formed by carbon atom losses at the ends of chain hydrocarbons, whereas norcarotenoids are formed by changes within the chain. For example, bixin an apocarotenoid with a molecular structure made up of 25 carbon atoms [14]. However, carotenes and xanthophylls are two classes of carotenoids that are both nutritionally and health-beneficial (Figure 2). The presence of a linear or cyclized hydrocarbon chain in one or both ends of the molecule characterizes the first class. Xanthophylls are oxygenated derivatives of carotenes, with 22 groups being: hydroxyl (β-cryptoxanthin), keto (canthaxanthin), epoxide (violaxanthin), and aldehyde (β-citraurine). The synthesis of carotenoids appears to be given little importance; however, it is through it that it is possible to distinguish the predominant carotenoid in a plant, flower, or fruit and, as a result, attribute its benefits in the context of public health promotion.

Figure 2: Same examples of carotenes and xanthophylls chemical strutures.

Functional relevance

Carotenoids are a class of fat-soluble pigments that include more than 1000 compounds, that present yellow, orange or red coloring [15]. The presence of conjugated double bonds in carotenoid structure contributes for their pigmentation, absorption of ultraviolet/visible radiation, and antioxidant activity but also is the main reason of their chemical instability. Considering that the chromophore action is related to its chemical structure, phytoene and phytofluene are known to be the only compounds free of pigmenting action. Without a doubt, the distinction of color spectra emitted by carotenoids is the most important in botanical terms. Among the different carotenoids, are distinguished lutein and zeaxanthin that give yellow or orange color to several common foods such as cantaloupe, pasta, corn, carrots, orange/yellow peppers, fish, salmon and eggs. However, as more studies were conducted, their bioactive effects were confirmed, and some are now considered nutraceuticals [2,8]. Lutein and zeaxanthin have demonstrated several beneficial health effects due to their capacity to act as antioxidants against reative oxygen species and also to bind with physiological proteins in humans [16]. According to Mrowicka., *et al*. [16] carotenoids are concentrated by the action of specific binding proteins such as StARD3, which binds lutein, and GSTP1, which binds zeaxanthin and its dietary metabolite, mesozeaxanthin. Thes authors also reported that supportive therapy with lutein and zeaxanthin can have a beneficial effect in delaying the progression of eye diseases such as age-related macular degeneration (AMD) and cataracts. Thus, lutein and zeaxanthin are potent filters of high energy blue light in both plants and animals, demonstrating their antioxidant capacity [17]. Canthaxanthin is a red-orange carotenoid that belongs to the xanthophyll group. This naturally occurring pigment is present in bacteria, algae and some fungi. This natural pigment was commonly used as a dye in animal feed. However, a recent scientific data report revealed that canthaxanthin may have health-promoting properties. Canthaxanthin enrichment of LDL has the potential to protect cholesterol from oxidation. In addition to its free radical scavenging and antioxidant properties (e.g., the induction of catalase and superoxide dismutase), canthaxanthin's immunomodulatory activity (e.g. enhancing the proliferation and function of immune competent cells) and its important role in gap junction communication (e.g. induction of the transmembrane protein connexin 43) have been reported [18]. Furthermore, because of its applications in the pharmaceutical, cosmeceutical, flavor food, and feed industries, biotechnological canthaxanthin production may provide an appealing industrial alternative that meets the growing demand to reduce costs and environmental pollution [19]. Another carotenoid pigment with several applications in the nutraceutical, cosmetics, food and feed industries is astaxanthin (red pigmentation), a ketocarotenoid synthesized by *Haematococcus pluvialis/lacustris*, *Chromochloris zofingiensis*,*Chlorococcum*, *Bracteacoccus aggregatus*, *Coelastrella rubescence*, *Phaffia rhodozyma*, some bacteria (*Paracoccus carotinifaciens*), yeasts, and lobsters, among other. Astaxanthin is closely related to other well-known carotenoids, such as β-carotene, zeaxanthin and lutein, thus they share many of the metabolic and physiological functions attributed to carotenoids. Thus, the structure of astaxanthin is very similar to that of lutein and zeaxanthin, however it possess a stronger antioxidant activity and UV-light protection effect [20]. Only natural astaxanthin is considered secure for human consumption. Due to its multiple applications in pharmaceutical, nutraceutical, cosmetics, dietary and aquaculture, astaxanthin is produced naturally by many companies due to its rapidly growing list of attributes [21]. However, chemically synthesized astaxanthin is not approved for direct consumption because of its chemical residues, which are not appropriate for humans, despite the fact that it is used for aquaculture [22]. Based on recent research, we conclude that *Haematococcus* astaxanthin supplementation could be a useful and beneficial strategy in health management.

This conclusion is supported by astaxanthin's strong antioxidant activity, potential role in health conditions in several human tissues, and the results of a user survey. Despite being recognized as a potent natural orange colorant, bixin is a carotenoid that receives little attention from the scientific community. The growing trend in the food industry to use new colorant sources, with health benefits combined with the demand of concerned consumers, makes it critical to find new colorant matrices that are safe for human consumption and exhibit high stability in the food products to be used. *Bixa orellana* L. is a worldwide known as a source of bixin. Although this tree is common in Brazil (Amazon), its fruit (annatto) was only recently introduced to Europe. According to Vilar., *et al*. [23], the colorant bixin accounts for approximately 80% of the total amount of colorants extracted from annatto seeds and can be further transformed into norbixin, a high added-value compound with several bioactive potential. The antioxidant activity of bixin has received more attention. *In vitro* tests revealed that seeds extracts possess higher ability to inhibit the action of oxygen reactive species (ROS), which is highly correlated with the presence of bixin. This plant has also been shown to have anti-inflammatory properties.

Despite differences in carotenoids' chemical structures, isomerizations, and bioavailability in foods, there is no doubt that carotenes (the most non-polar compounds) such as α-, β-carotene and lycopene are the most consumed carotenoids in the world's diet. According to the Physicians Committee for Responsible Medicine, these carotenoids have potent anti-cancer properties. The human body converts some carotenoids into vitamin A (β-carotene), which is required for normal vision and development [2]. Also, they are known to have anti-inflammatory and immune-boosting properties, and they are sometimes linked to the prevention of heart disease [24,25]. Lycopene, scientifically recognized as a nutraceutical compound, is thought to have a protective effect not only on the cardiovascular system but also on the prevention of cancer. It is extremely effective in the treatment of prostate, stomach, lung, and breast cancer. More importantly, this compound, in addition to suppressing neoplastic cell proliferation, induces programmed cell death and inhibits metastasis [25]. In addition, lycopene has neuroprotective properties, which makes it useful in the prevention and treatment of neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's [24].

Metabolism and bioavailability

Fat-soluble micronutrients, including carotenoids, have a digestion and absorption mechanism similar to lipids [26]. During digestion, emulsification begins with mastication and continues under the action of rhythmic gastric contractions. Partial hydrolysis occurs during this phase, which is initiated by lingual lipase and continued by gastric and pancreatic lipase. Carotenoids are then incorporated into mixed micelles composed of bile acids, free fatty acids, monoacylglycerols, and phospholipids. The micelles are in charge of transporting substances that are insoluble in water from the intestinal lumen to the enterocytes; this process occurs passively, through solubilization in the lipid layer of the enterocyte membrane [8,26]. Non-precursor carotenoids of vitamin A exit enterocytes via chylomicrons, where they are removed and passively absorbed by various tissues such as the adrenal, renal, adipose, splenic, lungs, and reproductive organs via the enzyme lipase lipoprotein. Vitamin A precursor carotenoids, such β-carotene and cryptoxanthin, may undergo oxidative cleavage to form retinoids (vitamin A). According to Kopsell and Kopsell [27] β-carotene is the most abundant carotenoid in the human diet, presenting the highest concentration found in many vegetable crops': leaf, fruit, and root tissues. Carotenoids, which are precursors to vitamin A, are partially converted to retinal and then to retinol in enterocytes, where it is esterified with fatty acids and grouped with neutral lipids (triacylglycerols, cholesterol esters, and phospholipids) to form the nucleus of chylomicrons [26,28]. These chylomicrons are then absorbed by the lymphatic system, enter the bloodstream, and are metabolized in the liver. Carotenoids are transported from the liver to tissues or organs primarily by very low density lipoproteins (VLDL-c) and low density lipoproteins (LDL-c) (LDL-c). However, the distribution of carotenoids among lipoprotein classes appears to be determined by individual physical characteristics of these as well as lipoprotein lipid composition, with less apolar carotenoids, such as xanthophylls, distributed in equal parts among high-density lipoproteins (HDL-c) and LDL-c and, to a lesser extent, VLDL-c [26].

The maximum levels of carotenoids in lipoproteins are affected 4 to 8 hours after these are consumed [29]. In fact, it is known that about 20 *carotenoids have* been identified in human blood and *tissues, being* α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene account for approximately 90% of plasma carotenoids. However, plasma contains only 1% of the body's carotenoids [30]. They are mostly stored in other organs and tissues. It should also be noted that the rate of absorption or transformation of carotenoids decreases linearly depending on the polarity of each carotenoid, so that the inverse of the logarithm of intake [7,8,30]. This decrease in potency with increasing intake can be viewed as a natural regulatory mechanism that prevents the organism from becoming intoxicated by excess.

Modulatory action of carotenoids

As is well known, free radicals are continuously produced during metabolic processes and act as mediators for electron transfer in various biochemical reactions, performing functions relevant to metabolism [31]. The formation of free radicals is a continuous and physiological action that fulfills essential biological functions through redox reactions. Although it is common to think of free radicals as molecules that are harmful to the human body, a small amount of free radicals is always required for metabolic maintenance. On the other hand, excessive production of these radicals promotes oxidative stress, which causes various types of cell damage, and its chronicity may be involved in the etiology or development of several diseases. In addition to premature aging, free radicals have been linked to the development of a variety of diseases, including heart disease, cancer, cataracts, Alzheimer's, diabetes, chronic inflammation, autoimmune diseases, Parkinson's, rheumatoid arthritis, and inflammatory bowel disease [31-33]. Depending on the exposure ratio, free radical attack on DNA, RNA, and proteins can result in cytotoxicity, allergies, mutagenesis, and/or carcinogenesis. In order to protect against the negative effects that excessive free radical production can cause, the organism develops defense mechanisms, with a focus on endogenous antioxidants, enzymes produced by the body, or exogenous antioxidants obtained from food [2]. As previously stated, the antioxidant properties of carotenoids are based on the chemical structure of each compound, primarily on conjugated double bonds and the presence of substituent groups in each carotenoid, making them antioxidant compounds against reactive oxygen species [16]. Therefore, carotenoids can act in three different ways: transfer of electrons ($CAR + ROO^{\bullet} \rightarrow CAR^{\bullet}+ + ROO$); removal of hydrogen ions ($CAR + ROO^{\bullet} \rightarrow CAR^{\bullet}+ ROOH$) or addition of radical species ($CAR + ROO^{\bullet} \rightarrow ROO\text{-}CAR^{\bullet}$) [15]. Thus, carotenoids can become radical species by acting on free radicals; these are normally stabilized by resonance and thus become unreactive. They can degrade in reactions with other radicals, producing stable products. Several factors, including carotenoid structure and cellular location, initial pigment concentration, degree of cellular integrity, presence or absence of enzymes and pro-oxidant and antioxidant substances, all interfere with carotenoids' antioxidant action. The ability of carotenoids to act as antioxidants is attributed to their protective capacity, with lycopene, canthaxanthin, -carotene, and lutein being the most potent. As in the case of lycopene, the opening of the -ionone ring increases the potential sequestrant. Hydroxyl group substitutions were shown to be less effective as deactivators. Similarly, epoxy and methyl groups have less of an effect, implying that carotenoids' properties are determined not only by the length of the system conjugate of double bonds, but also by the functional groups. The ability of carotenoids to act as antioxidants is attributed to their protective capacity, with lycopene, canthaxanthin, β-carotene, and lutein being the most potent. As in the case of lycopene, the opening of the β-ionone ring increases the potential sequestrant [34,35]. Hydroxyl group substitutions were shown to be less effective as deactivators. Similarly, epoxy and methyl groups have less of an effect, implying that carotenoids' properties are determined not only by the length of the system conjugate of double bonds, but also by the functional groups [36]. In fact, carotenoid consumption reduced the risk of lung cancer by 32% in nonsmokers, and it was also confirmed that smoking altered the concentration of many carotenoids, but not of lycopene, with an increase in lycopene consumption resulting in a reduction in cancer risk [22]. *In vitro* researches have shown that lycopene inhibits the proliferation of an oral cancer cell line [37,38]. Also, some clinical trials have shown low-density lipoprotein reductions (LDL-c), resulting from the oxidation of lycopene [39,40]. Thus, lycopene binds to LDL-c in plasma and may protect against atherosclerosis by inhibiting lipid peroxidation. The reduced activity of the HMG-CoA enzyme reductase, an enzyme important in the synthesis of cholesterol, is another mechanism for lycopene's protective effect against heart disease. As a result, lycopene consumption is inversely related to the risk of myocardial infarction.This has led to a rising interest in natural pigments as antioxidant supplements, with several studies reporting the potential of dietary antioxidant supplementation in health promotion [40]. Although lycopene's antioxidant properties are thought to be the primary reason for its benefits, some evidence suggests that other mechanisms are at work. Modulation of communication junctions of the type "gap" would be one of them, with cellular communication being essential for the coordination of biochemical functions in complex organisms and metabolic pathways, hormones, and the immune system.

In fact, several health-promoting functions of carotenoids have been identified, but not all of them are absorbed and used by tissues due to the fact that these compounds are not found free in foods, but rather associated with several plant cellular structures such as fibers, polysaccharides, and proteins. It is critical to disrupt the food matrix in order to these liposoluble compounds be absorbed, as this is the only way for them to be absorbed. As a result of the above mentioned, only a portion of the carotenoids are absorbed by intestinal epithelial cells and released as chylomicrons for blood circulation. Bioavailability is a key element in the absorption of these compounds by epithelial cells.

Bioavailability of carotenoids in human metabolism

Synergistic effects

The disruption of the food matrix, which can occur during the stages of digestion, which includes enzymatic action, mechanical and heat treatment, can increase the bioavailability of carotenoids. These procedures make it easier for the cell wall and organelles to be damaged, releasing the food's matrix-bound carotenoids and facilitating their distribution throughout the digestive system. According to Molteni., *et al*. [40], the bioavailability of carotenoids can range from 10% to 50%. This knowledge has been supported by other authors, including those who found that enzymatic treatment with cellulase and pectinases (used to break down the matrix of spinach) increased the plasma response of β-carotene in both genders aged between 18 and 58 years [41,42]. Other study showed that the consumption of spinach in the chopped form, rather than whole leaves, can increase by ~14% lutein content in the human plasma [43]. The absorption of these chemicals is also aided by heat treatment. Studies have indicated that high temperatures increase the bioavailability of the carotenoids found in tomatoes and/or products derived from them. The primary explanation for this phenomenon is that rising temperatures encourage the isomerization of carotenoids in foods from *trans* to *cis*, as well as breaking down the cell wall, which enables the extraction of carotenoids like lycopene [44,45]. *Cis* isomers are more bioavailable than *trans* isomers, probably due to their greater solubility, and therefore more easily incorporated into cellular micelles and, therefore better absorbed [8,45]. In another study, tomatoes that were heated to 88ºC for 15 minutes contained more lycopene content than in no heated tomatoes.

The presence of lipids in the diet, which are absorbed through the creation of micelles, is another element that improves the absorption of carotenoids in addition to heating. Solubilizing carotenoids in gut lipid micelles is also necessary to improve the absorption of these pigments [46]. Another factor that interferes with the bioavailability of carotenoids is their polarity. Xanthophylls (group to which belong to lutein and zeaxanthin) are less non-polar, while carotenes (such as β-carotene and lycopene) are more non-polar. Due to this fact, the low bioavailability of carotenoids is expected to the lack of solubility in the digestive fluid. Moreover, fats and oils have been known to increase the bioavailability of lipophilic compounds, while several reports have illustrate that intake of fats and oils enhanced the bioavailability of dietary carotenoids. One reason for this enhancement is the increased bioaccessibility of carotenoids by dispersing carotenoids in the digestive tract. Nagao., *et al*. [46] studied the effects of fats and oils on the bioaccessibility of carotenoids in vegetables using a simulated-digestion system. Blanched spinach leaves were digested with various lipids, and HPLC was used to measure the solubilized quantities of β-carotene, lutein, and -tocopherol. The bioaccessibility of β-carotene was enhanced by adding lipids in the following order: trioleoylglycerol < monooleoylglycerol < dioleoylglycerol and oleic acid. Furthermore, Liu and co-workers [47], using a gastrointestinal model, evaluated the different effect that oil type has on the bioaccessibility of carotenoids from yellow peppers. Medium-chain triglycerides (MCTs), long-chain triglycerides (LCTs), and indigestible orange oil (OO) were evaluated. Carotenoid bioaccessibility has been demonstrated to be influenced by oil type in the following order: LCT > MCT > OO > control (no oil). In another study, it was discovered that a day after eating cooked tomato sauce in oil, the serum concentration of lycopene in adult individuals increased by two to three times more, whereas fresh tomato sauce did not [48]. Consequently, the advantages of a synergistic interplay between dietary fat intake and improved carotenoid absorption, is observed. It is also verified that the amount of lipids ingested in diet contribute to the increase of absorption and consequently bioavailability of carotenoids in human metabolism. However, increasing the amount of lipids consumed does not ensure that all carotenoids are absorbed equally. These chemicals primarily increase the absorption of β-carotene, α-carotene, and lycopene (very lipophilic carotenoids), with little effect on xanthophylls (less lipophilic carotenoids like lutein and zeaxanthin).

Antagonistic effects

Several human and cell culture studies have been conducted to investigate the effect of carotenoid-carotenoid and carotenoid-nutrient interactions on carotenoid absorption. Those interactions may have antagonistic effects on the absorption capacity of all or some specific carotenoids. Food fibers can interfere negatively with the absorption of carotenoids. High molecular weight fibers, like pectin, inhibit micelles from forming, which increases the excretion of bile acids and total fat in the stool and, as a result, decreases the absorption of carotenoids generally [8,49,50]. Other factors may interfere with carotenoids digestion and absorption, such as in patients with pancreatitis insufficiency due to low lipase production and changes in intestinal pH, because pH below 4.5 reduces carotenoids solubilization and, as a result, absorption [51]. Vitamins play numerous well-established roles in human health. However, the impact of habitual dietary vitamin intake in glucose homeostasis in persons following acute pancreatitis remains unknown. Therefore, fat-soluble vitamins such as A and E, when ingested in high amounts, can negatively affect the absorption of carotenoids. Moreover, excessive amounts of other natural polar pigments (flavonoids) can compete with carotenoids and interfere with their absorption [52]. In addition to the issues directly related to dietary pattern, intestinal parasites can interfere with carotenoids absorption. *Ascaris lumbricoides* alters the shape of the intestinal mucosa and lowers fat absorption, thus interfering with carotenoids absorption.

Carotenoids applications

Food industry

For many years, the food industry has used artificial dyes to enhance the color of the items it processes, so improving their appearance. However, intake of these chemicals has been associated to a variety of side effects including hyperactivity, cytotoxicity, genotoxicity, and anxiety. Given the negative characteristics of synthetic additives and the amount of consumer understanding, the food sector has pushed for the adoption of products based on natural colors, which, while more expensive, ensure safety and, in many cases, offer functional properties. Examples include betalains, anthocyanins, and carotenoids, which can protect DNA, as well as hypoglycemic and antioxidant compounds.

The most common natural colours used in the food industries include annatto, curcumin, carmine and cochineal extracts, anthocyanins, and betalains [1]. The carotenoids commonly used for food coloring are astaxanthin, canyhaxanthin, β-carotene, lycopene, bixin, and norbixin.

Aquaculture and poultry

Carotenoids have been utilized as feed additives in poultry for the goal of coloring egg buds. Xanthophylls are the most commonly used, because they are absorbed and stored in the animal metabolism [53]. Capxanthin lutein, cryptoxanthin, canthaxanthin, zeaxanthin, and citranaxanthin are commonly utilized for this purpose, with canthaxanthin being the most commonly employed due to its high pigmentation efficiency, and approved by European Commission [54] for use in poultry diets. According to Grashorn [55] nearly 37% to 50% of the ingested canthaxanthin consumed is deposited in the yolk.

Because of the existence of integrated carotenoids throughout the food chain, certain shellfish such as shrimp, lobster, crayfish, trout, and salmon have meat that is orange to red in color. However, when fish and crustaceans are kept in captivity, carotenoids must be supplemented in the diet in order to increase and heighten the coloring of the meat. Astaxanthin, canthaxanthin, and a combination of these two pigments are the most commonly utilized carotenoids, even though astaxanthin is one of the most costly carotenoids utilized in the aquaculture industry [56].

Pharmaceutical, nutraceutical, and cosmeceutical industries

Color appearance, processing, and acceptability are all important in food, materials, and medications. Moreover, carotenoids have also been demonstrated to be effective in disease prevention through the action of free radicals. Photosensitivity disorders (erythema, polymorphous light eruption, protoporphyria erythropoietic), cardiovascular disease, diabetes, vision disorders (age-related macular degeneration, cataract), neoplasms (colon, esophageal, oral, pharyngeal, and laryngeal), neurological disorders, and immunological diseases are among the diseases caused by oxidative stress and can be prevented by carotenoids.

For example, β-carotene has been utilized as a tan enhancer and prolonger due to its buildup in the hypodermic tissue, which gives an intensity of color in the epidermis. Xanthophylls, such as lutein, accumulate in the macula lutea, protecting the eyes from cataracts and macular degeneration. A similar effect has been reported for zeaxanthin which also prevents macular degeneration. Some studies indicate that the oral administration of lutein and zeaxanthin is capable of protect the skin from the effects of UVB radiation. A study conducted by Sluijs., *et al*. [57] investigated an association of several carotenoids in the diet in preventing the incidence of type 2 diabetes, confirming a strong beneficial therapeutic interaction between α-carotene and β-carotene in the reduction of type 2 diabetes in men and women. Astaxanthin is, also, utilized in the nutraceutical and cosmetic industries, and it is occasionally used to fortify foods and beverages in some countries due to its significant antioxidative qualities and other health advantages. In fact, chemical synthesis of astaxanthin is currently the most cost-effective, and thus its synthetic preparations have dominated over 95% of the feed market. However, natural astaxanthin is used exclusively in the pharmaceutical, cosmetic, and food industries, because it is the only carotenoid that can pass through the blood-brain barrier, and it has been shown to have a number of important neuroprotective characteristics. According to Grand View Research [58] the global astaxanthin market in 2019 is expected to be worth USD 1.0 billion. Due to increased awareness of natural astaxanthin and its well-documented, multifaceted health advantages and safety, it is predicted to expand at a compound annual growth rate of 16.2% from 2019 to 2027, reaching USD 3398.8 million by 2027.

Conclusions

The minor difference in functional capabilities across carotenoids is due to differences in polyene chain length, conjugated double bonds involved, end group differences, and the presence of oxygen. At the locations of their conjugated double bonds, carotenoids exhibit E/Z (cis/trans) isomerism. The variation in their isomeric forms has a significant impact on their biological features such as bioavailability. When compared to *cis*-forms, all *trans*-forms are thermodynamically stable and prevalent in nature. In fact, humans can use them in nutraceutical foods, cosmetics, and food supplements, as well as for medical purposes. Carotenoids have a variety of health benefits, including antioxidant, anti-aging, and anti-cancer characteristics. It is a vitamin A precursor with a variety of therapeutic characteristics. Carotenoids are gaining popularity as nutritional supplements. Free radicals, cell redox imbalance, and oxidative stress have been linked to a wide range of human problems, including degenerative diseases. These compounds are powerful antioxidants that help to prevent or reduce the progression of chronic diseases, cellular damage, and aging. Also, they have been shown to reduce the risk of diabetes type 2, inflammatory diseases, heart disease, and cancer, obesity, chronic eye and macular diseases, parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease, and may be useful in the treatment of mental disorders. Despite all the benefits of these pigments, there is still little information about the synergistic and antagonistic factors in the bioavailability of carotenoids. This review article discusses the impact of chemical structures on carotenoids' production process, as well as their bioavailability in human metabolism and, as a result, their biological effects. Further studies are suggested to promote the bioavailability of carotenoids in human metabolism, suggesting their nanoencapsulation in order to protect them from environmental conditions, increase their shelf life, or to mask component attributes such as undesirable flavors. Functional compounds in small capsules are the future in the food and medical field.

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