nutraceuticals

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Review

Enhancing Carotenoids' Efficacy by Using Chitosan-Based Delivery Systems

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Abstract: Carotenoids represent a large group of well-known substances, mainly due to their nature as pigments and their beneficial effects on human health. These compounds are found naturally in microorganisms and plants but are not produced by humans, who must consume them through their diet. However, the mere intake of foods containing even large quantities of carotenoids is insufficient to guarantee their optimum absorption and, therefore, the desired beneficial effects. Due to their physicochemical characteristics, carotenoids are poorly stable and mostly insoluble in polar solvents like water. The conservation and improvement of their properties have become crucial objectives for the nutraceutical and functional food sector. Increasingly innovative delivery systems are being tested and developed. In this context, chitosan, a polysaccharide derived from the deacetylation of chitin, available in the exoskeleton of crustaceans and insects and the cell wall of some fungi and marine microalgae, has proved to be highly advantageous. In this review, we summarize the main characteristics of carotenoids, their benefits on human health, and their bioaccessibility and bioavailability for humans. We analyze the most recent carotenoid delivery systems, focusing on the potential of chitosan in preserving and enhancing the beneficial effects of these valuable pigments.

Keywords: carotenoids; nutraceuticals; efficacy; delivery systems; chitosan

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1. Introduction

Carotenoids are secondary metabolites present in microorganisms (bacteria, yeast, fungi, and microalgae) and higher plants. They cannot be produced by the human organism. In nature, their principal role is to attract different light wavelengths and transfer their energy to chlorophylls, a function occurring mainly in photosynthetic organisms. Moreover, they can act as photo-protectors, precursors of hormonal substances, antistress secondary metabolites, and attractive agents in plant–insect interaction [1,2].

In humans, the beneficial effects of carotenoids have been widely investigated, including protection against oxidative stress, beneficial properties for eyesight, UV protection for the skin, anticancer properties, the enhancement of cognitive function, and prevention against age-related degenerative diseases, cardiovascular diseases (blood pressure), and obesity [3]. Some carotenoids (i.e., β-carotene, α-carotene, and β-cryptoxanthin) are precursors of vitamin A, a vitamin that, among other things, supports vision, immune function, development and growth, and reproduction.

In recent years, the knowledge of the beneficial aspects of carotenoids has grown and so has, in parallel, the awareness of the need for adequate dietary intake [3]. The recommended intake of carotenoids depends on the compounds, age, and gender of people [4]. Therefore, it is necessary to increase their absorption through proper supplements.

The nutraceutical sector is seeing the expansion of a huge market of functional foods enriched with carotenoids from conventional foods or alternative sources such as microalgae. It is estimated that the carotenoid market could reach almost USD 1.9 billion in 2027, with prices ranging from USD 300 to 3000 per kg for cheaper carotenoids, such as β-carotene, and up to 10,000 USD/kg for carotenoids that remain very expensive, such as astaxanthin [5].

There are more than 1000 types of natural carotenoids that require further research about their properties and sources. Carotenoids are chemically unstable and easily degradable under environmental conditions—such as high temperature, oxygen, light, and pH—during food processing, storage, and gastrointestinal digestion [6]. Moreover, due to their lipophilic nature, carotenoids are poorly soluble in an aqueous medium. This low water solubility limits their application in aqueous-based foods and beverages [7]. All of these physicochemical aspects make carotenoids poorly bioaccessible and bioavailable, where bioaccessibility refers to the portion of carotenoids available for intestinal absorption after release from the food, and bioavailability refers to the fraction of administered carotenoids that reaches the bloodstream without undergoing chemical changes [7–9].

Therefore, carotenoids should be incorporated into suitable delivery vehicles to overcome these limitations. Various delivery systems were proposed for carotenoids, including micro/nanoencapsulation via emulsions, powders, capsules, micelles, hydrogel, and so on [8]. Each system presents advantages and disadvantages and should be chosen considering its targets and applications.

Chitosan-based delivery systems are strategic for strengthening carotenoids' stability, bioactivity, and bioavailability [9–13]. Chitosan is a biological and cationic polysaccharide, mainly extracted from crustacean chitin by deacetylation. Structurally, it consists of N-acetyl D-glucosamine and 2-amino 2-deoxy-β-D-glucopyranose units. The deacetylation degree and molar mass determine its properties and applications. In particular, the chitosan deacetylation degree influences many of its applications, including biomolecule delivery [14,15]. Therefore, chitosan has unique physicochemical and biological properties such as biocompatibility, biodegradability, bioactivity, low toxicity, mucoadhesion, and structural variability [9–13]. As a result of these remarkable properties, chitosan is used in a wide range of fields, such as medicine, dental care, food processing chemistry, biotechnology, agriculture, and environmental protection [14,15].

Chitosan-based carriers allow for better dissolution into food products and enhance carotenoid accessibility and availability in the intestinal tract. Moreover, they also preserve carotenoids from chemical degradation, ideally maintaining their nutritional value even after processing, storage, and digestion of the food matrices [9,16,17]. Two classes of chitosan-based nanocarriers are commonly used in carotenoids' encapsulation, lipid-based and biopolymeric nanocarriers [9]. Chitosan has been investigated in lipid-based delivery systems for coating nanoemulsions and nanoliposomes. Instead, in biopolymeric delivery systems, it has been used alone or in combination with other polysaccharides to produce polysaccharide-based vehicles and biopolymeric nanogels [18–24].

Given the great importance of this topic, the present updated review discusses the health benefits of carotenoid intake, as well as several factors limiting the bioaccessibility and bioavailability of these bioactive molecules. The review then examines new developments in delivery systems and finally focuses on the most promising chitosan-based carriers designed to improve carotenoid availability.

2. Carotenoids

2.1. Physicochemical and Biological Properties

Carotenoids are secondary metabolites found in plants, algae, and some microorganisms, such as bacteria, yeasts, and molds. They are pigments ranging in color from yellow, orange, and red to purple in the case of some carotenoids, such as Rhodobacterioxanthin and Phillipsiaxanthin, present in some microorganisms.

More than 1000 carotenoids are present in nature [1]. In plants, carotenoids perform several essential functions. They are crucial in the photosynthetic process and play a relevant role in the protective mechanism against damage from light and oxygen. Moreover, carotenoids act as signals to attract pollinators and seed dispersers. Finally, they are precursors of relevant apocarotenoids (i.e., carotenoids' derivatives), such as vitamin A and the phytohormones abscisic acid and strigolactones [25].

Chemically, carotenoids are pigments made up of isoprene units (C5) repeated 6, 8, 9, or 10 times to obtain molecules of 30, 40, 45, and 50 carbon atoms, respectively. Different terminal groups are present at the ends of the skeleton chain, including acyclic, cyclic (e.g., cyclohexane or cyclopentane), or aryl groups formed via the cyclization of the linear precursor [2]. The most abundant carotenoids in nature are C40 (Figure 1).

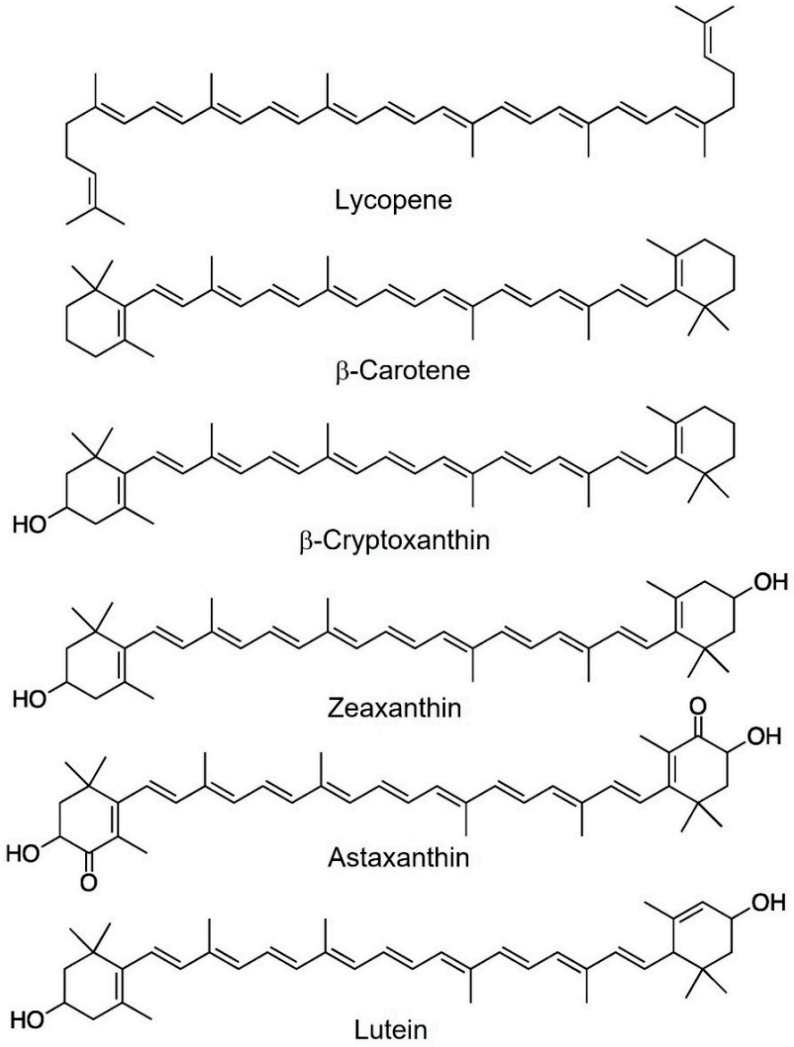

Figure 1. Most abundant carotenoids in human blood.

Carotenoids are divided into two main classes: carotenes, i.e., compounds containing only carbon and hydrogen; and xanthophylls, that is, carotenoids containing oxygen. Carotenes include β-carotene and lycopene, while xanthophylls include zeaxanthin, astaxanthin, and lutein [26].

The presence of substituents containing oxygen (hydroxyl, keto, methoxy, and oxo groups) gives polarity to the xanthophylls and makes them slightly hydrophilic. For this reason, carotenes are lipid-soluble pigments but insoluble in polar solvents. On the contrary, xanthophylls are soluble in polar solvents (like alcohols) and nonpolar solvents (like ether and hexane) [27].

The conjugated double bonds of the isoprenoid structure are the basis of the many functionalities of carotenoids, starting from the colorant capacity and ending with the antioxidant properties of removing free radicals and the singlet oxygen [26,28].

The biological properties of carotenoids depend on many factors beyond the presence of the polyene chain and its length. These factors include the presence of functional groups and their placement (e.g., α and β), acyclic and cyclic structure, and (E)- or (Z)-configuration [29].

Furthermore, the polyunsaturated chain of carotenoids can undergo various reactions mediated by light, oxygen, heat, catalysts, and free radicals, such as oxidation, isomerization, hydrolysis, and degradation. These reactions can lead to the formation of products with diminished or completely absent biological properties [30]. In light of this poor stability, it is necessary to find suitable systems to preserve the beneficial functions of carotenoids when they can come into contact with chemical agents, light, heat, or are extracted from their starting biological matrix.

The physical and chemical properties of carotenoids make them able to function both in plants, where they are produced, and in humans, who intake them through their diet [31].

Over the years, many studies have demonstrated the ability of carotenoids to have various effects on human health. Table 1 provides a summary of these effects.

Table 1. Effects of carotenoids on human health.

Health Effects	Specific Effects	Carotenoids	References
	Prevention and mitigation of age-related macular degeneration (AMD) and cataracts	Lutein and Zeaxanthin	[32,33]
	Delayed onset and mitigation of diabetic retinopathy	Lutein, Zeaxanthin, Lycopene	[34–36]
Antioxidant activities	Diabetes and osteoporosis	Lycopene	[37]
	Mitigation of multiple sclerosis and atherosclerosis	β-Carotene	[26]
	Prevention of age-related disease	Astaxanthin	[38]
	Protective effect on the skin	β-Carotene, Lutein	[39,40]
	Inhibition of retinal impairment	Lutein and Zeaxanthin	[41]
Cancers	Inhibition of lung cancer	Lutein, Astaxanthin and b-Cryptoxanthin	[42–44]
	Inhibition of risk for prostate cancer	Lycopene	[39,43,45]
	Mitigation of risk for colon-rectal cancer	Lycopene	[43,46]
	Mitigation of non-alcoholic fatty liver disease (associated with hepatocellular carcinoma)	Lycopene	[47]
	Mitigation of risk for breast cancer	Lutein and Zeaxanthin Lycopene	[46,48,49]
	Mitigation of risk for non-melanoma cancer	Lutein, β-Carotene, α-Carotene, Lycopene, Zeaxanthin, Astaxanthin, Lutein, Cryptoxanthin, Lycopene, Fucoxanthin	[50,51]
	Mitigation of risk for melanoma	β-Carotene	[52,53]
Cardiovascular diseases		Lycopene	[44,46,54]
		Astaxanthin and b-Carotene	[55,56]
	Effects on HDL and LDL cholesterol levels	Phytoene and Phytofluene	[57,58]
	Reduction in the severity of cardiovascular disease	Lutein and Zeaxanthin	[59]

Table 1. *Cont.*

Health Effects	Specific Effects	Carotenoids	References
	Antihypertensive and anti-aggregative Effect	Lycopene	[60]
	Reduction in immune activation (In patients with cardiovascular disease)	β-Carotene	[61]
Neurological disorders	Regulation of lipid raft formation in neuronal cells (proper membrane fluidity)	Lutein and Zeaxanthin	[62]
	Protection for neurodegenerative diseases and For neurological, cognitive, and psycho-behavioral disease conditions	Lycopene	[63,64]
Bacterial infections	Inhibition of bacteria cells growth	β-Carotene, b-Cryptoxanthin, Lutein, Violaxanthin, Antheraxanthin, Fucoxanthin, Zeaxanthin	[65]
Others	Improvement of sleep quality and duration	Lycopene	[66]
	Anti-inflammatory properties	Lycopene	[67]
	Cognitive performances	β-Carotene and Lutein	[33,68,69]
	Bone homeostasis	β-Cryptoxanthin	[70]

The effects of introducing carotenoids into the human diet on vision and vision-related diseases have long been known and supported by clinical, epidemiological, and interventional studies [71]. Most of the beneficial effects of carotenoids on human health are due to their antioxidant characteristics, which is why they are used in various fields and to hinder the progression or mitigate the effects of numerous diseases [3].

The physical characteristics of carotenoids, namely their tendency to aggregate even in different solvents, affect their antioxidant abilities through interactions with reactive oxygen species and other antioxidants such as tocopherol and vitamin C [31].

These pigments play an important role in counteracting certain types of cancer: the carotenoids' complex anticancer properties are associated with phosphorylation and activation of the major kinases, modulation of cellular pathways of Nrf2 and NF-κB transcription factors, apoptosis, cell cycle progression, intercellular gap junction communication and angiogenesis [63]. Carotenoids are helpful in this area because, at present, most anticancer drugs have serious side effects, and resistance and toxicity problems. Therefore, new alternatives are always being sought. In addition to having a direct antitumorigenic effect, carotenoids can serve as a natural scaffold for other phytochemicals able to manage and treat certain types of cancer [63].

A key role is played by β-carotene as a precursor of vitamin A. Only carotenoids with an unsubstituted b-ionone ring have pro-vitamin A activity, and, among them, the most abundant in the human diet and tissues is β-carotene. Vitamin A (or retinol) is a potent gene regulator that controls the expression of nearly 700 genes. It is also critical for vision and plays an essential role in lipid metabolism, thus putting obesity under control [3].

Carotenoids and their cleavage products, such as retinoids and apo-carotenoids, positively affect adipocyte differentiation. Through various mechanisms, this eventually leads to a reduction in abdominal and subcutaneous fat. In addition, due to antioxidant activity, carotenoids can reduce the overall oxidative load or decrease its accumulation, thus also exerting beneficial effects on weight management and obesity [39].

The main transcriptionally active form of vitamin A is retinoic acid (or acidic vitamin A), which, under normal conditions, is present only in small amounts in tissues [3]. The importance of vitamin A is evident from the consequences of its deficiency, which, in developing countries, is a major public health problem. In these countries, vitamin A deficiency mainly affects preschool children and pregnant women, and can cause blindnesspoor growth, and sometimes even death [70,72,73]. The beneficial effects of carotenoids on the health of postmenopausal women are manifold and studied, above all, in Eastern countries. Some

authors report a positive correlation between β-carotene intake and increased lumbar spine bone mineralization (understood as mineral density) in postmenopausal Korean women [39]. Sugiura et al. (2012) investigated the possible correlation between serum carotenoid levels and bone loss in postmenopausal Japanese women [74]. The research study showed an inverse association, thus suggesting a protective action of carotenoids on bone tissue. Umigai et al. (2020) have shown that the carotenoid intake of paprika suppresses bone resorption, helping to maintain high bone quality in postmenopausal women [75].

Carotenoids, such as lutein and zeaxanthin, are crucial for children's visual and cognitive development and are the main carotenoids in human milk. Several studies showed that lutein is more bioavailable in human milk than in infant formula. This fact affects postnatal brain development. In total, 75% of the infant's brain growth occurs in the first year of life, doubling during the third trimester. At these stages, lutein and zeaxanthin are in brain regions specialized for visual processing, memory, learning, and language. In particular, lutein is up to 3–4 times more present than other carotenoids in these brain regions [39,76].

In addition, several carotenoids also have effects on cognitive function in adults. The mechanism is still unclear. It may be related to antioxidant activity. For example, placebo-controlled studies suggest that dietary supplementation of lutein or lutein plus zeaxanthin may positively affect cognitive function in older men and women [39]. On the other hand, lycopene is one of the most potent antioxidants that effectively neutralize reactive oxygen species and is an effective natural neuroprotective agent. Therefore, it is widely studied as a candidate for providing therapeutic benefits and maintaining brain health in neurological, cognitive, and psycho-behavioral diseases. For example, it helps fight neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [77]. These diseases (Parkinson's disease, amyotrophic lateral sclerosis-ASL, stroke, Alzheimer's disease, and Huntington's disease—to name only the major ones) are characterized by progressive neuronal depletion and apoptosis, resulting in cognitive, motor, and intellectual dysfunction. However, it is still unclear how biochemical changes lead to neurodegeneration. It is only known that central nervous system inflammation and immune activation are implicated in the pathophysiology of neurodegenerative diseases. Thus, the development of therapies for these diseases is very challenging. Indeed, there are currently no cures for degenerative diseases: available remedies can only slow or delay their onset. In this context, the effects of a molecule such as lycopene, with high neuroprotective abilities, and of carotenoids in general, which promote synaptogenesis and neurogenesis, are very promising [63].

Studies regarding the role of lipophilic compounds, to which carotenoids belong, in cognitive neuroscience and aging are also extremely interesting. Carotenoids have crucial biological effects on proper brain function and brain robustness maintenance and promote healthy aging. Of course, a rigorous and objective assessment of these effects must consider the multifactorial nature of aging and nutrigenetics, geographical, social, and cultural aspects [78].

Another notable aspect is the influence of carotenoids on sleep quality and duration. In particular, the link between sleep quantity/quality and diet, specifically the intake of lycopene-rich fruits/vegetables, has been investigated. In reality, to provide a robust figure regarding the impact of a lycopene-rich diet on sleep, fruit/vegetable-containing foods would have to be disaggregated in the dietary records of the subjects surveyed. Even with this limitation, studies have shed light on the link between dynamic parameters of sleep biology and a lycopene-rich diet, showing a strong correlation that deserves further deeper investigation [77].

A study of the effects of dietary carotenoid supplementation, whatever the desired upshot, must take into account multiple interactions with other (micro)nutrients and involve a broader spectrum of robust biomarkers of antioxidant status and free radical-induced damage [78].

Unfortunately, numerous studies conducted on carotenoids have suggested an overly simplistic idea of their use. There is the belief that because β-carotene is present in healthy diets and has antioxidant effects in vitro, high doses of this carotenoid can only amplify the beneficial effects on health [31]. This assumption does not consider the interaction with other dietary components or their actual bioavailability and bioaccessibility.

2.2. Dietary Sources and Bioaccessibility/Bioavailability

The human body cannot synthesize carotenoids; therefore, the only way to take advantage of their beneficial effects is to introduce them through the diet [1]. Carotenoid content in the food may vary depending on growing years and areas, cultivars, processing techniques, and storage conditions. The foods richest in β-carotene are certainly sweet potatoes and carrots. According to Arscott (2013), the average β-carotene content in sweet potatoes is 91.8 μg/g FW (fresh weight), while in carrots, it is 88.4 μg/g FW [79]. Other foods with excellent β-carotene content are apricot (66.4 μg/g FW) and spinach (55.9 μg/g FW). The latter, along with broccoli, are the foods with the highest lutein content. Spinach contains an amount of lutein equal to 119.4 μg/g FW and broccoli 34.4 μg/g FW, respectively. On the other hand, the highest amount of lycopene is contained in tomatoes (30.2 μg/g FW), watermelon (23.83 μg/g FW), and grapefruits (17.51 μg/g FW) [80]. Although carotenoid content in foods is essential for human health, their limited absorption is a critical factor in exploiting their countless benefits. Unconventional sources, such as carotenogenic microorganisms and microalgae, have been explored to study the production, content, properties, and bioavailability of carotenoids [80]. The scientific interest in unconventional sources is due to the contribution they could make to the growing demand for healthy, sustainable, and available food for all and an exponentially growing population.

In Table 2, some food sources and unconventional sources were selected as representative of the highest quantity of β-carotene [79].

Table 2. Average concentrations of carotenoids in foods and unconventional sources.

Carotenoids	Sources	Concentration	References
β-carotene	Sweet potato	91.8 μg/g FW	[79]
	Carrot	88.4 μg/g FW	[79]
	Apricots	66.4 μg/g FW	[79]
	Spinach	55.9 μg/g FW	[79]
	Beet greens	34.4 μg/g FW	[79]
	Tomato	3.4 μg/g FW	[79]
	Cassava root, Sweet yellow	7.27 μg/g FW	[79]
	Squash	3.7 μg/g FW	[79]
	Zea mais	0.17 μg/g DW	[79]
	Dunaliella salina (microalgae)	34,100 μg/g DW	[81]
	Blakeslea trispora (fungi)	59,910 μg/g DW	[82]
	Phaffia rhodozyma (yeast)	42.81 μg/g DW	[83]
Lutein	Spinach	119.4 μg/g FW	[79]
	Broccoli	34.4 μg/g FW	[79]
	Tagetes flowers	2930 μg/g DW	[59]
	Scenedesmus almeriensis (microalgae)	3040 μg/g DW	[84]
	Chlorella sp.	7000 μg/g DW	[85]
Lycopene	Tomato	30.2 μg/g FW	[79]
	Grapefruit	17.51 μg/g FW	[79]
	Watermelon	23.83 μg/g FW	[79]
Astaxanthin	*Haematococcus pluvialis* (microalgae)	20,000 μg/g DW	[81]
	Phaffia rhodozyma (yeast)	400 μg/g DW	[86]
	Xanthophyllomyces dendrorhous (yeast)	5000 μg/g DW	[87]
	Shrimps, prawns, crabs (waste residues)	57.5 μg/g DW	[88]

Among the most promising unconventional sources of carotenoids, the microalgae *Dunaliella salina* was selected for its β-carotene production of 34,100 μg/g DW [81]. *Dunaliella salina* can accumulate β-carotene up to about 10% DW (dry weight). *Blakeslea trispora*, on the other hand, is among the most studied microorganisms belonging to the fungi genus for β-carotene production. Some authors produced up to 59,910 μg/g DW through studies on improving β-carotene biosynthesis and optimizing the production process using 35 mM sodium acetate [82].

At the industrial level, the most widely used natural source of lutein is the petals of the flower of the plant *Tagetes erecta* with an average content of 2930 μg/g DW [85]. New sources of lutein include the microalgae species *Scenedesmus almeriensis*, which can accumulate about 3040 μg/g DW [84] and whose production has been optimized to achieve 5700 μg/g DW [89]. Other microalgae species belonging to *Chlorella* species, such as *C. sorokiniana*, *C. minutissima*, and *C. vulgaris*, can produce 5000 to 9000 μg/g DW of lutein through the optimization of autotrophic and heterotrophic growth processes [85].

Haematococcus pluvialis is the microalgae that most accumulates the super antioxidant astaxanthin, up to 5% of its dry weight. Other species can produce astaxanthin as *Chlorella zofingiensis* (0.7% DW) and *Nannochloropsis oculata* (2% DW) [90,91] but their content is significantly lower than that of the species *Haematoccocus pluvialis.*

The red yeast *Xanthophyllomyces dendrorhous* can accumulate up to 5000 μg/g DW of astaxanthin [87]. *Phaffia rhodozyma* yeast is recognized by both the FDA and EFSA as a GRAS additive in feed as a source of astaxanthin [92]. *Phaffia rhodozyma* wild type can produce up to 200–400 μg/g DW of astaxanthin but engineered strains are being experimented with to achieve higher yields for industrial applications [83]. Some authors recently demonstrated a biorefinery process using *Phaffia rhodozyma*, that produces up to 63.11 μg/g DW of astaxanthin and 42.81 μg/g DW of β-carotene. Other promising sources of astaxanthin are shrimp's, prawns', and crabs' residue/wastes such as heads, shells, tails, and exoskeletons, from which astaxanthin, protein, and chitin can be extracted by using several technologies [93]. Astaxanthin can be recovered by using conventional extraction methodologies, such as solvent extraction, or unconventional technologies, such as microwave, ultrasound, and supercritical fluid extraction, to reach a content of around 100 μg/g DW [88]. As mentioned, although searching for unconventional sources of carotenoids is essential to increase the intake of these substances, the limiting factor remains their absorption in the intestine.

Indeed, due to their apolarity and lipophilic properties (high octanol–water partition coefficients, log P_{oct} > 8), their absorption in the intestinal tract is very poor. Only 5–30% of carotenoids are absorbed. Some key steps, such as micellarization, are necessary for their absorption in the gut [94]. In vitro studies on micellarization and uptake by Caco-2 cells demonstrated that lutein and phytoene incorporate in micelles better than lycopene and β-carotene [46].

Micellarization is crucial for the absorption of fat-soluble compounds such as carotenoids. After their separation from the food matrix, carotenoids are included in the fat fraction of the food, which facilitates biliary and pancreatic secretion. The following gastric emulsification into lipid droplets enables the incorporation of carotenoids into mixed micelles, consisting of bile salts, lysophospholipids, free cholesterol, and mono-acyl-glycerides produced via lipolysis and digestion of their esters and triglycerides. These micelles, which do not have the same apolarity problems as carotenoids, easily pass through the epithelial cells of the gastrointestinal lumen where the carotenoids, once desorbed from the micelles, can be absorbed into the ileum. These mixed micelles are very interesting for researchers because they may be used to enhance the carotenoids' bioaccessibility and absorption [95]. Chacón-Ordóñez et al. (2019) studied the natural bioaccessibility of carotenoids in some foods using in vivo, ex vivo, and in vitro models. They reported that the highest relative bioaccessibility of β-carotene was from pineapple (96.5%) and kiwi (55%), while, among vegetables, it was from carrots (14%), and broccoli (17%). In the case of lutein, the highest bioaccessibility is

from watermelon (49%), spinach (22%), and chicory (27%). The bioaccessibility of lycopene is 2% for tomatoes, while it can reach 33% for the gac fruit [96].

Another significant aspect that can strongly influence the bioavailability of carotenoids is their distribution in foods. Carotenoids in plant foods and colored plant foods are embedded in more complex chloroplast–protein structures than carotenoids in animal foods such as eggs and dairy products, in which they are more bioavailable [97].

Carotenoid separation from the food matrix can be enhanced via various processes of food matrix processing, cooking, and heating that can improve the release of carotenoids from food by weakening the cell walls and making the matrix more attackable by enzymes [74]. Koh et al. (2018) demonstrated that the bioaccessibility of β-carotene in pumpkin and butternut squash increased in fried samples compared to raw matrices, from around 10.56% to 69% in pumpkin and from 2% to 22% in butternut squash [98].

Assessing the bioaccessibility and bioavailability of carotenoids is complicated because of several factors involved, including dietary aspects concerning fat/lipids in meals, dietary fiber content, especially pectin, and the effect of divalent minerals. One solution may be to mimic and accentuate what happens during digestion.

On the effect of fat/lipids on carotenoids' bioaccessibility, some authors demonstrated via in vivo digestion tests of tomato pulp how the bioaccessibility of lycopene can increase from about 2% to 10% by using the fat of oils such as olive or sunflower [99].

Some authors evaluated the bioaccessibility of β-carotene using a gastrointestinal model study (INFOGEST) testing different concentrations of droplet oils. They observed an increase in the bioaccessibility of β-carotene as the oil concentration increased, achieving up to 93% bioaccessibility with a 10% oil concentration. Finally, the amount of oil did not affect the stability of β-carotene [100]. It has been shown that carotenoids have low bioaccessibility caused by their interaction with other compounds such as dietary fiber [101,102]. Among dietary fiber, pectin has negative effects on lipolysis, thus affecting the bioavailability of carotenoids. The molecular characteristics of pectin, such as molecular weight, degree of methyl esterification, viscosity, and hydrophobicity, influence the lipid digestion process. In particular, the interaction of pectin with bile salts can reduce the micellarization process, thus altering the bioavailability of carotenoids [103]. The intake of bivalent minerals such as calcium, magnesium, and other micronutrients at the dietary recommended doses can inhibit the micelle formation process and carotenoid incorporation. Bivalent minerals may interfere with the absorption processes of carotenoids by causing the precipitation of bile salts and lipids needed in the emulsification processes of carotenoids [104]. Some authors observed that high concentrations of bivalent minerals such as calcium (500 mg/L) and magnesium (around 300 mg/L) negatively affected bile salt precipitation and micelles' stability [98,105]. The bioaccessibility of carotenoids can also be improved via pasteurization processes. Aschoff et al. (2015) demonstrated an increase in bioaccessibility from about 10.8% β-carotene in orange pieces to about 40% in pasteurized juice [106]. Another process that improves carotenoid bioaccessibility is dehydration, as observed for total carotenoids in a chickpea and amaranthus mixture [107]. Thermal processes can enhance the release of carotenoids from food. However, in most cases, heat-sensitive carotenoids can undergo degradative processes. Astaxanthin, for example, has poor stability, as it is very sensitive to light and temperature and undergoes degradation processes even at prolonged exposure to room temperature up to about 7% thermal degradation [108]. Isomerization processes could also affect bioaccessibility. In vitro digestion model studies show a difference in astaxanthin bioaccessibility between its trans and cis isomers [109].

Another aspect crucial for the potential activity of carotenoids as a drug-like agent concerns their pharmacokinetics, i.e., the processes that condition the achievement and maintenance of an adequate concentration of drugs in the various compartments of the human body. The assessment of pharmacokinetics in carotenoids is complex. A SLAMENGHI-defined systemic approach is followed, which includes the most important factors such as the type of carotenoid, molecular binding, quantity, initial matrix, the implementer of absorption and bioconversion, the physiological state and the genetic factors of the

host, and the synergy of all these factors [110]. The mechanisms involved in carotenoid pharmacokinetics are absorption in the gastrointestinal tract, distribution in plasma and tissues, metabolism in the liver and excretion in the kidneys for elimination. Clinical trials showed that β-carotene bioconversion to retinol appears to be dose-dependent with a typical dosage of 15–50 mg/day [111]. Several studies on β-carotene absorption and distribution in mice have shown that β-carotene in its free form does not enter the circulatory system. It is distributed in the stomach or remains predominantly in the chyme. On the contrary, β-carotene transported via nanoemulsion is better distributed and metabolized in the liver [112]. According to some authors, lutein-free, administrated orally to male rats at a dose of 10 mg/kg body weight, reached its maximum concentration in plasma after about 2 h, and it accumulated more in the mesenteric fat deposits than in the liver [113]. The concentration in plasma is also enhanced when lutein is encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanoparticles. Lycopene contained in food is partially released via chewing through mechanical and enzymatic action, then packaged in chylomicrons and transported to the lymphatic system. In the lymph, the chylomicrons are degraded, passively releasing the lycopene before it is eliminated by the liver [114,115]. Pharmacokinetic studies on healthy adult men showed that the bioavailability of astaxanthin administered at 40 mg was around four times higher for lipid-based supplements than that of commercial formulations [116]. Other studies on animal models have shown that astaxanthin administered in different formulations is more distributed in the spleen [117].

Based on the above, carotenoids' chemical properties and the factors influencing their pharmacokinetics make it necessary to increase the bioaccessibility, stability, and solubility of carotenoids using novel delivery systems such as nanocarriers composed of biopolymers, polysaccharides, and protein- or lipid-based carriers.

3. Delivery Systems for Carotenoids

The hydrophobicity of carotenoids is a drawback for their integration into functional beverages and food products with high water content. Nevertheless, carotenoids could be properly micro/nano-encapsulated to be enveloped by a wall material. Various polymers can be used as wall materials and protect carotenoids from extreme external conditions, such as acidity, heat, oxidization, light, and moisture. Carotenoids could be loaded in lipid–biomacromolecular compounds, where lipids improve the properties of numerous biomacromolecules, including proteins and polysaccharides [118].

Carotenoids are usually micro-encapsulated via emulsification, coacervation, spray drying, freeze-drying, and extrusion. Due to carotenoids' lipophilic nature, oil-in-water (o/w) emulsions are often used as delivery systems before spray drying with linseed oil as a carrier, and a binary blend of gum Arabic and maltodextrin (1:1 w/w) as wall materials. Unfortunately, lycopene was considerably degraded during spray-drying, and β-carotene was almost undetectable throughout the gastric phase of simulated gastrointestinal digestion [119]. Oil-in-water micro- and nanoemulsions were produced to encapsulate carotenoids extracted from halophilic Archaea. The results showed their effectiveness as delivery systems [120]. For commercial applications, the liquid form should be converted into a powdered form, e.g., via spray- or freeze-drying [121].

As an alternative to microparticle-based carriers [122], nanocarriers are potential delivery systems for carotenoids. The interest in nanoencapsulation is constantly increasing because nanocarriers (<100 nm) offer a high efficiency of encapsulation, loading capacity, solubility, bioavailability, stability, and dissolution rate, thus improving carotenoids' absorption [123]. Nanocarriers can be grouped into two main classes, biopolymeric nanocarriers and lipid-based nanocarriers, as summarized in Table 3.

Table 3. Different nanocarriers (NC) for the nanoencapsulation of carotenoids.

Nanocarriers			Encapsulation Technique	Encapsulated Carotenoids	Ref.
Biopolymeric NC	Polysaccharide-based NC	Chitosan	Nanocapsules	Lutein	[124]
			Nanoemulsions	β-carotene	[125]
			Nanoparticles	β-carotene	[126]
				Crocin	[127,128]
				Lutein	[129,130]
				Lycopene	[131]
			Nanostructured lipid carriers	Fucoxanthin	[132]
		Alginates	Nanocapsules	β-carotene	[133]
			Nanoparticles	β-carotene	[134]
				Crocin	[127,128]
			Nanohydrogel	β-carotene	[135]
		Starches	Nanoemulsions	β-carotene	[136–139]
				Lycopene	[140]
		Cellulose	Nanocapsules	Lutein	[141]
			Nanomicelles	β-carotene	[142]
		Pectins	Nanoemulsions	Crocin	[143]
				Lutein	[144]
	Protein-based NC	Whey proteins	Nanocapsules	β-carotene	[145]
			Nanodispersions	β-carotene	[146]
			Nanoemulsions	β-carotene, lutein	[136,144,147–151]
				Crocin	[143]
			Nanoparticles	β-carotene	[152–154]
				Lycopene	[155]
			Solid lipid nanoparticles	β-carotene	[156,157]
		Caseins	Nanoemulsions	β-carotene	[151]
				Lutein	[158]
			Nanomicelles	β-carotene	[159]
			Nanoparticles	β-carotene	[160,161]
		Gelatin	Nanodispersions	Astaxanthin	[162]
			Nanoemulsions	Lutein	[144]
		Soy proteins	Nanoemulsions	β-carotene	[163]
			Nanoparticles	β-carotene	[153,164]
			Solid lipid nanoparticles	β-carotene	[156]
		Cereal proteins	Nanoparticles	β-carotene	[165]
		Potato proteins	Nanoparticles	Astaxanthin	[166]
Lipid-based NC	Nanoemulsions			β-carotene	[167–172]
				Lutein	[148,150,158,173–178]
				Lycopene	[140,179–181]
	Nanoliposomes			β-carotene	[182–184]
				Lutein	[185–187]
				Lycopene	[188,189]
	Nanoniosomes			β-carotene	[190]
				Lycopene	[191,192]
	Solid lipid nanoparticles			β-carotene	[157,193,194]
				Lutein	[178]
				Lycopene	[195–197]
	Nanostructured lipid carriers			Astaxanthin	[198]
				β-carotene	[199–201]
				Lutein	[178,202–204]
				Lycopene	[197,205,206]

Among various nano delivery systems, colloidal nanocarriers are emergent promising delivery systems. Among them, liposomes are commonly used for the encapsulation of carotenoids and other bioactive compounds in the food industry. Nevertheless, liposomes are thermodynamically unstable and unsatisfactory during storage and incubation in biological fluids. The formation of bioadhesive and polymeric layers can improve liposome performances. For this reason, composite phospholipid-chitosan vesicles (chitosomes) has been proved as effective delivery systems for bioactive compounds [207].

4. Chitosan-Based Delivery Systems for Carotenoids

4.1. Chemical Characteristics and Functional Properties of Chitosan

Chitosan is a natural polysaccharide composed of random distributions of N-acetyl-D-glucosamine (GlcNAc) and d-glucosamine (GlcN), with GlcN imparting its cationic properties at neutral/physiological pH [208]. It derives from full or partial deacetylation of N-acetyl-D-glucosamine-containing chitin (Figure 2).

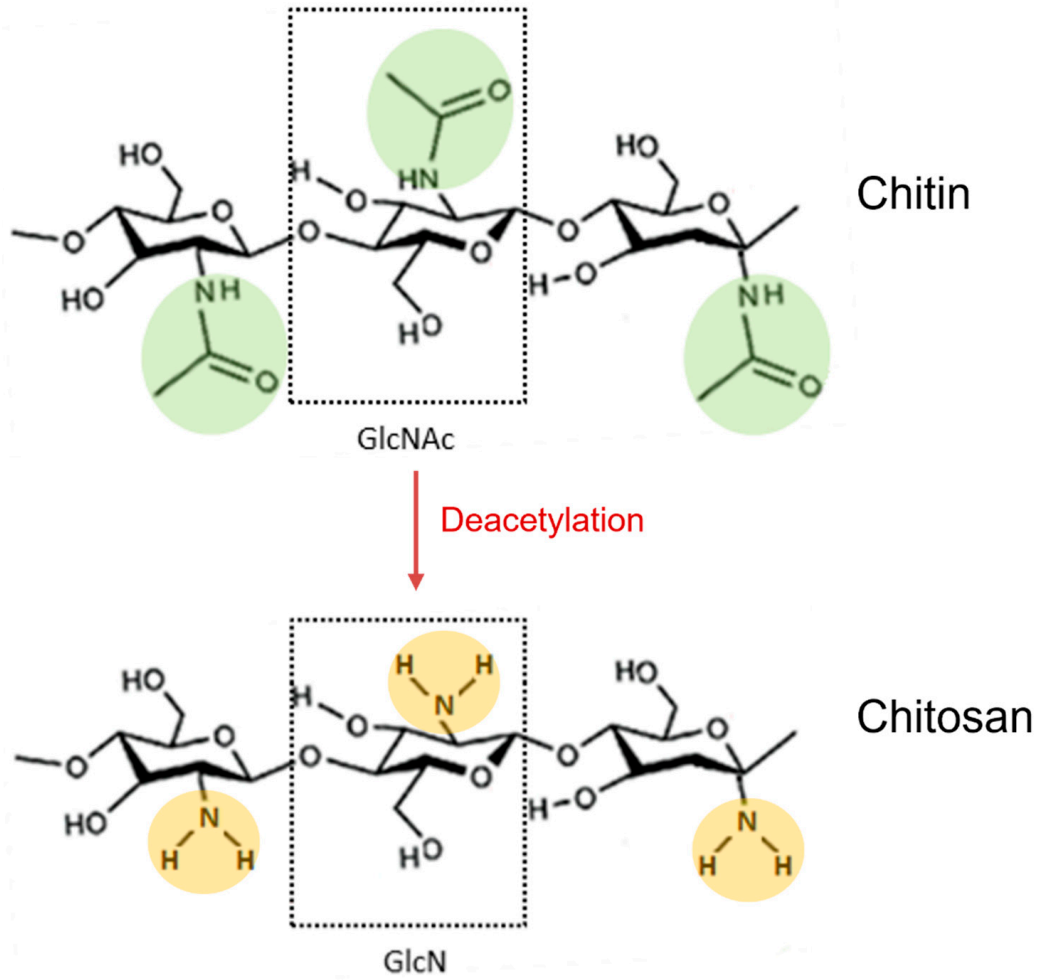

Figure 2. Deacetylation reaction of chitin to obtain its fully deacetylated derivative chitosan. N-acetylglucosamine (GlcNAc) and glucosamine (GlcN) monomers are shown in dotted boxes; the acetamido groups of chitin are highlighted in green, while the amino groups of chitosan are highlighted in orange.

Currently, the most common commercial source of chitin and chitosan is the exoskeletons of crustaceans [209]. Chitin and chitosan also occur in nature in fungal cell walls and insects [210].

Chitin deacetylation can be achieved chemically or biologically. The conventional chemical methods under high-concentration alkaline conditions are the most widely used,

but their environmental impact and high cost prevent their scaling up and industrial application [14]. An alternative chemical method for chitin deacetylation relies on the use of the green solvent glycerol, a recyclable and stable by-product of biodiesel. Nevertheless, it has drawbacks since it requires high temperatures for an extended period [211]. Applying microwaves or ultrasounds can accelerate chitin deacetylation, thus reducing extraction times and chemical solvent concentration [14].

The biological method employs chitin deacetylase enzymes derived from fungi and bacteria. Due to its mild reaction conditions, it is an eco-friendly alternative to chemical methods. Despite this, high enzyme costs and long reaction times limit this process's scaling up [212].

Chitin becomes chitosan when it is deacetylated to a deacetylation degree (DDA) of 50% [213,214]. DDA indicates the percentage of D-glucosamine units to the total monomer units (i.e., D-glucosamine and N-acetyl-D-glucosamine) in the chitosan polymer chain. DDA plays a major role in influencing chitosan's physicochemical properties, such as solubility, flexibility, crystallinity, conductivity, viscosity, and surface tension [215]. In this way, DDA affects chitosan's biological properties and performance in many applications [216,217]. A 70–96% DDA and molecular weight of 1000–2500 kDa are typical of commercial chitosan [218].

Chitosan has unique characteristics, such as biodegradability, biocompatibility, low toxicity, and low allergenicity [219,220]. It exhibits many biological activities, such as antioxidant, anti-inflammatory, antimicrobial, antitumoral, hypocholesterolemic, blood anticoagulant, etc. [221].

Chitosan contains native amine groups that are positively charged; hence, it is a natural cationic biopolymer in water at pH < 6. The positive charge enables the interaction with negatively charged molecules, including phospholipids, fatty acids, proteins, DNA, RNA, and anionic polysaccharides, such as carrageenan and alginate. The cationic form explains its antimicrobial, gelling, and coating properties. Moreover, chitosan occurs negatively charged at alkaline pH due to the hydroxyl groups of its D-glucosamine units. In the anionic form, it can chelate various metal cations, including copper, iron, and cadmium [222]. In addition, primary amino and hydroxyl groups of chitosan are fundamental reactive sites for its easy conversion to other derivatives, such as phosphorylated chitosan, quaternary ammonium chitosan salts, carboxymethyl chitosans, and many other substituted chitosans [223].

4.2. Chitosan Nanocarriers for Effective Delivery of Carotenoids (as Advanced Delivery Systems)

Chitosan exhibits numerous functional properties, making it well suited to a wide range of applications from chemical and agrochemical industries to pharmaceutical, medical, and cosmetic industries, food and nutrition industries, textile and paper industries, etc., as summarized in Table 4.

Table 4. Applications of chitosan in different fields.

Field	Chitosan Applications	Form
Agriculture	Biofertilizer and biocontrol agent (time release of products) Booster of plant growth and plant production Controlled agrochemical release Frost protection Modify plant-microbial interactions Pesticide formulations Soil conditioner Stimulator of crop yield Stimulator of secondary metabolites to induce plant defenses	Solution Film Powder Spray Coating Gel Powder Nanoparticle

Table 4. *Cont.*

Field	Chitosan Applications	Form
Aquaculture	Removal of organic/inorganic compounds Removal of bacteria Removal of ammonia Functional food Micro-carrier for bioactive compounds Probiotics Drugs microencapsulation Drug delivery Oral delivery (vaccination) Antimicrobial and antioxidant	Microsphere Bead Powder
Pharmaceutical and medical/biomed	Excipients Gene, drug, and vaccine delivery system Antimicrobial agent (antibacterial, antifungal) Anti-inflammatory, antiulcer, and antihypertensive agent Dermatological products Hydrating agents Nutraceutical ingredient Hemostatic and anticoagulant compound Antitumor agent and tumor inhibition Anti-HIV agent Innate immune cell recruitment and activation agent Treatment of leukemia, diabetes Sutures, surgical threads, bandages, sponges Biocompatible and biodegradable materials for use as implants, blood substitutes, blood vessels or wound dressing material Dental implants Contact lenses Magnetic resonance imaging	Solution Powder Tablet Nanoparticle Nanocomposite Sponge Gel and hydrogel Microsphere Capsule and microcapsule Bead Film Fiber and nanofiber
Food and nutrition	Additives for human and animal Antibacterial, antifungal, antioxidants Astringency Diet foods and dietary fibers Edible films Hypolipidemic and hypocholesterolemia activities Infant feed ingredient Prebiotics	Solution Film Blend Coating Bead
Cosmetic	Antistatic effect Bacteriostatic Body cleaning products Encapsulating agent Functional additives Hydrating and film-forming agent Products for hair care Products for oral/dental care Products: shampoos, creams, lotions, nail polish, make-up powder, etc. Skin delivery formulations Thickening agent	Solution Film Powder
Environmental	Adsorbent/biosorbent Antibacterial material Antifouling agent Coagulant/flocculant Interactions with proteins and amino acids Material for treatment of contaminant water Polymer for ultrafiltration Reduce odors	Adsorbent/biosorbent Coagulant/flocculant Antifouling agent Interactions with proteins and amino acids Reduce odors Polymer for ultrafiltration Material for treatment of contaminant water Antibacterial material

Table 4. *Cont.*

Field	Chitosan Applications	Form
Textile	Dye-binder for textiles Impregnated textile materials Binding agent for non-woven Surface modification of textiles Textiles with anti-bacterial properties Textile antimicrobial finishing Sanitary fibrous products Surgical threads Textile preservative and deodorant agent Non-allergenic fibers	Microcapsule Fiber Gel and gelatinous dispersion Coating
Paper and pulp	Wet strength agent Reduction in paper water vapor permeability Antibacterial and antimicrobial protective coating for paper packaging Antitermite in papermaking Retention and drainage agents Biodegradable packaging Wrapping and toilet paper Carbonless copy paper Cardboard Chromatography paper Modification of cellulose fibers Photochromic paper Papermaking wastewater treatments	Nanoparticle Powder Coating
Biotechnology and chemistry	Adhesive activity between metallic surfaces Analytical reagent Binders for silicon/graphite Biosensors, electronic and electrochemical devices Cell-recovery composite electrodes in lithium-ion batteries Corrosion protection of aluminum Enzyme and cell immobilization Ionic liquids and deep eutectic solvents Matrix for chromatography Membranes for lithium batteries Metabolic Analysis of biological fluids Permeability control Protein separation Reverse osmosis Solvent separation Transport direction of target molecules	Powder Bead Nanoparticle Microsphere Sponge Coating Fiber Solution Ionic liquids Membrane Sensors Composite Blend

Based on [14,212,217,224–229].

Chitosan can be easily functionalized to develop a highly effective delivery system for food ingredients, nutraceuticals, drugs, genes, and vaccines due to its several properties, including biocompatibility, bioactivity, mucoadhesive ness, high charge density, and non-toxicity [10,208,230,231].

Developing delivery systems for food ingredients and nutraceuticals implies the use of GRAS substances (generally regarded as safe), which must be recognized previously as suitable for human consumption, for example, by the EFSA (European Food Safety Authority) in Europe or by the US FDA (United States Food and Drug Administration) in the USA [9,13]. Chitosan is recognized as GRAS and approved for dietary use in Italy, Japan, and Finland [232]. Chitosan-coating treatments significantly retarded enzymatic browning on the surface of fresh-cut fruits and vegetables during storage, extending their shelf life and preserving their quality attributes [216]. Moreover, the polycationic nature of chitosan makes it one of the most potent antimicrobials, capable of inhibiting a wide range of microorganisms, including Gram-negative and Gram-positive bacteria, as well

as yeast and mold [233]. Four main mechanisms are implicated in chitosan's ability to kill microorganisms [14,216,233], as shown in Figure 3.

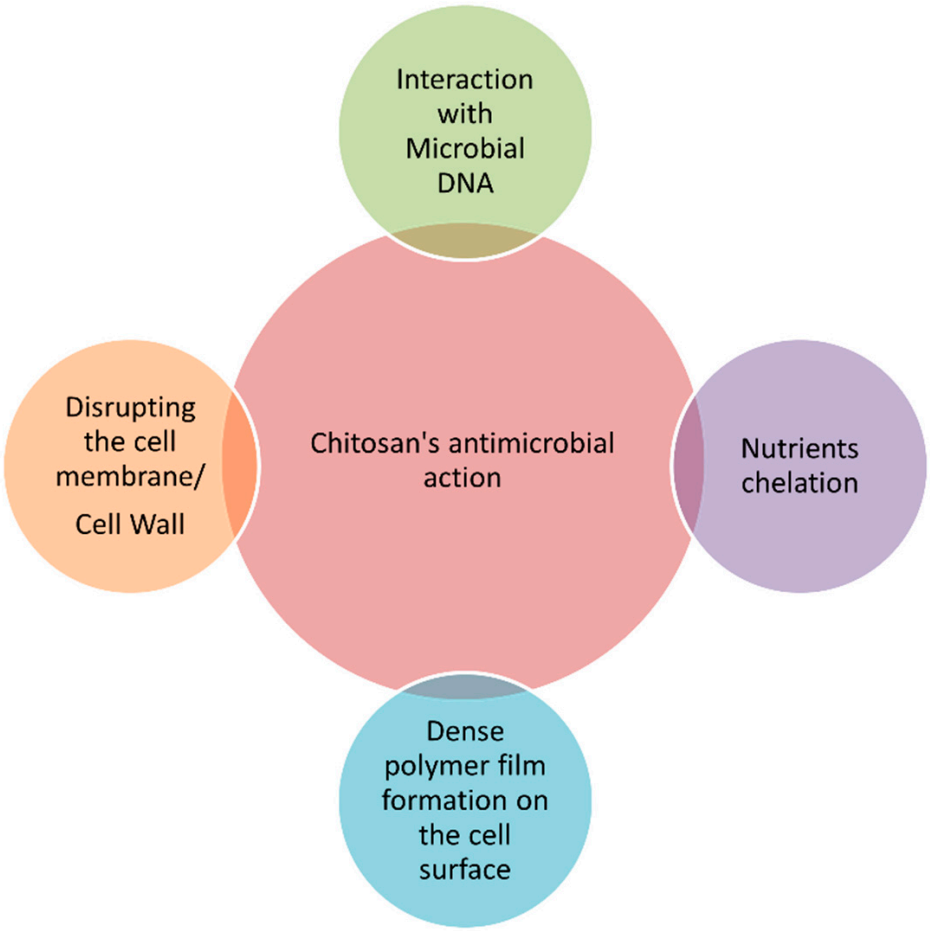

Figure 3. Main mechanisms of action of chitosan against microorganisms.

Carotenoids' incorporation into chitosan-based delivery systems has been shown to benefit these nutritional components [13,232]. Carotenoids' biological activity is heavily influenced by preserving their bioavailability or the fraction of an ingested compound that is absorbed and available for physiological functions (i.e., enters the systemic circulation in an active form) [13]. Several factors can compromise carotenoid bioavailability, including insufficient gastric residence time, low permeability and/or solubility within the gastrointestinal tract, and instability [13,234]. As a result, chitosan-based delivery systems improve the stability, bioactivity, and bioavailability of carotenoids, and control their release, thus increasing their efficacy. [9–13].

Two types of chitosan-based delivery systems are widely employed for carotenoid encapsulation: lipid-based and biopolymeric systems [9]. In lipid-based delivery systems, chitosan has been extensively studied as a coating material to make nanoemulsions and nanoliposomal vehicles designed for greater solubilization and micellarization of the carried carotenoids than the crystalline form in which they are found in plant tissues [235] (Rostamabadi et al., 2019). Adding chitosan to nanoemulsions and nanoliposomes protects encapsulated compounds and controls their release [236]. Biopolymeric delivery systems include polysaccharide-based and biopolymeric nanogels [9,237]. Several techniques can be used to prepare biopolymer nanoparticles developed for carotenoid delivery, including emulsification, desolvation, coacervation, and electrospray drying [238].

Figure 4 shows nanomaterials developed using chitosan for application as carotenoid delivery systems.

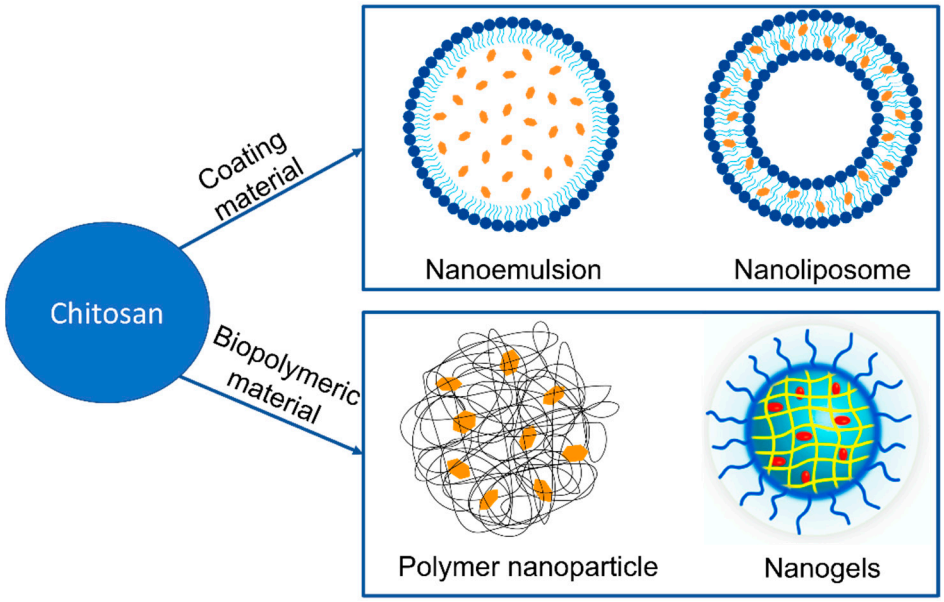

Figure 4. Nanomaterials developed using chitosan for application as carotenoid delivery systems.

Table 5 summarizes some chitosan-based delivery systems used for the encapsulation of carotenoids.

Table 5. Chitosan-based delivery systems for encapsulating carotenoids.

Delivery System	Carotenoids	Particle Size (nm)	Encapsulation Efficiency (%)	Storage Stability (Days)	Ref.
Chitosan-coated Nanoemulsion	β-carotene	218; 143.7	NA	21 at 37 °C	[18]
Chitosan-coated Nanoliposomes	β-carotene, Lutein, Lycopene, Canthaxanthin	70 to 100	75	NA	[239]
Chitosan (Polysaccharide)-Based Nanocarriers	β-carotene	NA	>95	NA	[240]
Chitosan-based Nanogels	Fucoxanthin	200 to 500	47 to 90	6 at 37 °C	[241]

NA = Not applicable.

4.2.1. Chitosan-Coated Nanoemulsions

Nanoemulsions (NEs) represent an effective bioactive molecule delivery system for enhancing physicochemical stability, water dispersibility, and bioavailability [9,242]. Small droplet sizes and improved functional properties characterize these kinetically stable colloidal systems. The most employed NEs are oil-in-water (o/w) and water-in-oil (w/o) types, although multiple emulsion types ($o/w/o$ and $w/o/w$) are also used occasionally [242].

Baek et al. (2020) [18] employed chitosan to coat β-carotene-loaded NEs obtained by mixing an appropriate proportion of β-carotene (10 mg), medium chain triglycerides oil (10%), Tween 80 (4.5%), lecithin (4.5%) and deionized water (80%). This mixing was undergone via high-speed homogenization at 5000 rpm for 10 min and probe sonication for 40 min. The prepared β-carotene NEs were then mixed with 2% water-soluble chitosan (WSC) in a 1:1 ratio, obtaining water-soluble chitosan-β-carotene NEs (WSC-BC-NEs) with a mean particle size at 218 nm. Compared to uncoated β-carotene NEs, WSC-BC-NEs showed enhanced stability, exhibiting β-carotene retention of 82% or 77.6% as well as improved thermal stability by 45.1% or 28.6% after 21-day storage at 37 °C or 21-day UV light exposure at room temperature, respectively. Then, using chitosan to coat nanoemulsions successfully increased both the thermal and UV light stability of the encapsulated β-carotene. The zeta potential of the coated nanoemulsions (WSC-BC-NEs) shifted from negative to positive after chitosan coating and was high (+40 mV), suggesting a stable nanoemulsion [18].

Therefore, water-soluble chitosan coating could be an effective strategy in the food industry to produce β-carotene emulsions with enhanced stability.

4.2.2. Chitosan-Coated Nanoliposomes (Chitosomes)

Nanoliposomes are nanoscale colloidal structures formed by concentric phospholipid bilayered vesicles and an aqueous core [11]. Due to their amphiphilic nature, they are versatile structures that can incorporate and carry both hydrophilic and hydrophobic molecules, separated or simultaneously [243]. Hydrophilic molecules can be located in the aqueous core, whereas hydrophobic molecules can be found between the two phospholipid layers [9]. Nanoliposomes have a smaller size and a higher surface-to-volume ratio than macro- and micro-liposomes. These characteristics can improve the bioaccessibility, bioavailability, and stability of the encapsulated compounds [244]. Finally, they are biocompatible, biodegradable, and well suited for carotenoids' encapsulation and delivery [245,246]. Tan et al. (2014) [247] effectively encapsulated carotenoids, including lutein, β-carotene, lycopene, and canthaxanthin, in nano liposomal structures and assessed their bioaccessibility. Lutein exhibited the highest bioaccessibility, followed by β-carotene, lycopene, and canthaxanthin. Due to their encapsulation in liposomes, these carotenoids also showed an increase in their antioxidant activity in the following order: lutein > β-carotene > lycopene > canthaxanthin [247]. As recently as 2020, Hamadou et al. successfully developed β-carotene-loaded marine and egg phospholipids nanoliposomes. The nanoliposomes produced using marine phospholipids were smaller, better at inhibiting lipid peroxidation, and stable at 4 °C for 70 days [245].

However, nanoliposomal particles suffer from drawbacks related to the stability and leakage of the encapsulated compound during storage or digestion, which limits their applicability [248]. Using chitosan as a coating material appears to be a promising approach for nanoliposomal surface modification aimed at improving stability during processing and in gastrointestinal conditions. As an example, conventional nanoliposomes are susceptible to gastric pH and enzymatic degradation. Then, a polymeric coating based on chitosan could enhance the bioavailability of ingredients absorbed in the intestine and protect the bioactive during food processing in which some conditions, such as temperature and pH, are employed [236].

Hybrid systems containing chitosan-coated nanoliposomes are known as "chitosomes" [249]. Tan et al. (2016) [239] successfully developed 70–100 nanometer-sized chitosomes by combining nanoliposomes with chitosan to encapsulate four kinds of carotenoids, specifically lycopene, β-carotene, lutein, and canthaxanthin. Chitosan was flatly adsorbed onto nanoliposome membrane surfaces via electrostatic attraction, inducing charge inversion but maintaining the nanoliposome spherical shape. Chitosan linked to the nanoliposomal surface prevents lipid molecules from moving freely, enhancing their ordering at the polar headgroup region and hydrophobic core of the membrane. These rigidifying effects enhanced nanoliposome stability against heating (at 37 °C for 6 h, 65 °C for 30 min, and 90 °C for 30 s), gastrointestinal stress (0.06–0.31% release over 4 h), and centrifugal sedimentation. The authors have also demonstrated that chitosomes' encapsulating and retaining ability is highly dependent on the molecular structures of carotenoids. As a result, the liposomal membrane preserved β-carotene and lutein more efficiently than lycopene and canthaxanthin [239]. This study suggests that chitosomes could be used to deliver bioactive compounds in nutraceuticals and functional foods.

4.2.3. Chitosan-Based Nanocarriers

Using chitosan as a polysaccharide biopolymer to bind a poorly soluble bioactive molecule enhances the molecule's stability and keeps it from degrading [250]. Furthermore, polysaccharide-based nanocarriers are more stable at high temperatures than lipid- or protein-based nanocarriers, which melt or denature at high temperatures [251].

Table 6 summarizes different studies testing the encapsulation of carotenoids in nanocarriers based on chitosan as a polymer.

Table 6. Summary of different studies testing the encapsulation of carotenoids in nanocarriers based on chitosan as a polymer.

Delivery System	Biopolymer	Loaded Compound	Findings	Ref.
Polysaccharide-based nanocarrier	Chitosan	Lutein	Bioavailability improved by 27.7%. Postprandial levels in blood plasma (54.5%), liver (53.9%), and eyes (62.8%) in mice higher than control.	[21]
	Poly (ethylene oxide)-4-methoxycinnamoylphthaloyl-chitosan (PCPLC)/ poly(vinylalcohol-co-vinyl-4-methoxycinnamate) (PB4)/ ethylcellulose (EC)	Astaxanthin	In PCLC: high encapsulation efficiency (98%), loading (40%), and high stability to heat. No positive results with PB4 or EC encapsulation	[20]
	Chitosan + sodium tripolyphosphate/ chitosan + carboxymethylcellulose	β-carotene	Chitosan + sodium tripolyphosphate carrier: high β-carotene release in aqueous media and gastric fluid, and adequate release in intestinal fluids. Chitosan + carboxymethylcellulose carrier: efficient release in aqueous media and gastric fluid; small release in intestinal fluid. β-carotene release enhanced in food systems with both carriers.	[240]

Arunkumar et al. (2013) [124] developed water-soluble low-molecular-weight chitosan (LMWC) nanoencapsules with lutein to improve the bioavailability of this carotenoid. This study obtained particles ranging in size from 80 to 600 nm. Both in vitro and in vivo tests revealed that the bioavailability of lutein enclosed in LMWC nanoencapsules was significantly higher than the non-encapsulated control. Postprandial lutein levels in the plasma (54.5%), liver (53.9%), and eyes (62.8%) of mice fed on nanoencapsulated lutein were higher than those found in mice fed on non-encapsulated lutein [124]. Based on the results of this study, LMWC could be used as a carrier to enhance lutein bioavailability and as an efficient dietary compound in food and pharmaceutical applications.

Tachaprutinun et al. (2009) [20] evaluated astaxanthin encapsulated into the following three different polymers: poly (ethylene oxide)-4-methoxycinnamoylphthaloyl-chitosan (PCPLC), poly(vinylalcohol-co-vinyl-4-methoxycinnamate) (PB4), and ethylcellulose (EC). PCPLC led to a high encapsulation (98%) and loading (40%) efficiency. Moreover, astaxanthin-loaded PCPLC exhibited high stability when heated for 2 h at 70 °C in an aqueous environment. By contrast, EC failed to encapsulate astaxanthin, while PB4 showed low encapsulation efficiency. Both suffered complete degradation upon heating [20].

Rutz et al. (2016) [240] encapsulated β-carotene in microparticles formed by chitosan/sodium tripolyphosphate or chitosan/carboxymethylcellulose. The authors evaluated the performance of these microparticles in food systems by analyzing the carotenoid release profile under simulated gastric and intestinal conditions. A higher than 95% encapsulation efficiency was achieved. Chitosan/sodium tripolyphosphate-coated microparticles yielded approximately 55%, while chitosan/carboxymethylcellulose-coated microparticles yielded 87%. In water and gastric fluid, chitosan/carboxymethylcellulose-encapsulated particles showed optimal release behavior, while their release in the intestinal fluid was low. When applied to food systems, these particles produced enhanced carotenoid releases in the intestinal fluid, but they released low amounts of carotenoids during storage. In contrast, chitosan/sodium tripolyphosphate carriers provided adequate β-carotene release

in aqueous media and gastric fluid, as well as an acceptable release in intestinal fluids. Like its counterpart, β-carotene released from these carriers was enhanced when incorporated into food systems. Conversely, these carriers released more β-carotene during storage [240].

4.2.4. Chitosan-Based Nanogels

Chitosan can be used as biopolymeric material to prepare nanogels that are dispersions of hydrogel nanoparticles derived from physically or chemically cross-linked polymeric networks [19,252]. Nanogels represent next-generation drug delivery systems due to their ability to encapsulate drugs efficiently, ease of preparation, and low toxicity [252].

Chitosan-based nanogels are synthesized by reacting amino groups on chitosan in aqueous droplets with an ionic crosslinker, such as tripolyphosphate (TPP), or chemical crosslinker, such as glutaraldehyde [253].

Ravi et al. (2015) [254] developed chitosan–glycolipid nanogels loaded with fucoxanthin (Fx) by using an ionic-gelation method with polymeric chitosan dispersed in glycolipid (GL) as a carrier. Fx is a marine xanthophyll carotenoid present in brown algae that exhibits antioxidative properties. In this study, nanoencapsulation improved the bioavailability of Fx. Furthermore, the authors investigated the adverse effect of acute and sub-acute toxicity of chitosan nanogels (CS-NGs) loaded with Fx + GL in rats, determining that the CS-NGs are safe for delivering Fx even at higher doses [254]. In addition, Ravi and Baskaran (2015) used an ionic gelation method to develop fucoxanthin-loaded chitosan–glycolipid hybrid nanogels (Fx-CH-GL NGs) composed of chitosan and glycoside (1:0.5 *w*/*w*), sodium tripolyphosphate in water (0.03%) and fucoxanthin (1 mg). Fx-CH-GL-NGs were demonstrated to have higher stability and bioavailability in vitro (68%) than those of standard Fx (51%) and Fx + GL (35.5%) [241].

5. Conclusions

The consumption of foods rich in carotenoids has beneficial effects on health, including boosting the immune system to fight infection and reducing the risk of cancer, cystic fibrosis, cardiovascular diseases, COVID-19, macular degeneration, etc. The food and pharmaceutical industries are particularly interested in carotenoids due to their multifaceted functions, including their role as provitamin A, their potent antioxidant properties, and their ability to quench reactive oxygen (ROS) and lipid peroxidation within the cell membrane's lipid bilayer. Nevertheless, because of their lipophilicity, carotenoids are poorly soluble in an aqueous medium and chemically unstable. Food processing, storage, and gastrointestinal transit can trigger carotenoid degradation under various environmental conditions. Moreover, carotenoids have poor oral bioavailability. Therefore, their use in aqueous-based foods is limited. Because of all this, appropriate delivery systems are essential to increase carotenoid solubility, stability, and bioavailability. Chitosan, a linear and cationic polymer obtained from chitin deacetylation, has been proven and utilized as a biopolymer for the construction of effective drug nanocarriers, such as nanoemulsions, liposomes, polysaccharide nanoparticles, and nanogels. Recently, several research studies demonstrated that chitosan-based delivery systems can significantly increase the bioavailability, stability, and efficacy of carotenoids. However, further research is required to study the safety and efficacy of carotenoids using chitosan-based delivery systems. In fact, some chitosan-based delivery systems could have limited effectiveness due to processing difficulties.

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