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The potential modulation of gut microbiota and oxidative stress by dietary carotenoid pigments

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Abstract:

Gut microbiota plays a crucial role in regulating the response to immune checkpoint therapy, therefore modulation of the microbiome with bioactive molecules like carotenoids might be a very effective strategy to reduce the risk of chronic diseases. This review highlights the bio-functional effect of carotenoids on Gut Microbiota modulation based on a bibliographic search of the different databases. The methodology given in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) has been employed for developing this review using papers published over two decades considering keywords related to carotenoids and gut microbiota. Moreover, studies related to the health-promoting properties of carotenoids and their utilisation in the modulation of gut microbiota have been presented. Results showed that there can be quantitative changes in intestinal bacteria as a function of the type of carotenoid. Due to the dependency on several factors, gut microbiota continues to be a broad and complex study subject. Carotenoids are promising in the modulation of Gut Microbiota which favoured the appearance of beneficial bacteria, resulting in the protection of villi and intestinal permeability. In conclusion, it can be stated that carotenoids may help to protect the integrity of the intestinal epithelium from pathogens and activate immune cells.

Keywords: Gut microbiota, carotenoid, carotene, xanthophyll, diet, intestine

1. Introduction

Over the last few years, obesity has become a pandemic due to the immensity of complications and morbidities (such as type 2 diabetes and cardiovascular diseases (CVDs)). There is a consensus that both genetic and environmental factors are involved in overweight or obesity (Blüher 2019). Therefore, it is not enough to increase physical activity and/or make a caloric decrease in our meals to deal with it (Carrera-Quintanar et al. 2018; Ji et al. 2020; Yin et al. 2019). With this in mind, developing and developed communities have experienced a growing interest in healthier lifestyles, particularly the consumption of nutritious foods. This reflects what has worried the scientific community and professionals in recent decades to prevent non-communicable diseases. When it comes to having an optimal diet, it is not only important to make a good choice of products for consumers, but also how to get the most out of the absorbed nutrients so that they exert a positive effect on the cells, tissues, organs, and organ systems of the body (Carrera-Quintanar et al. 2018; Ji et al. 2020; Yin et al. 2019).

In addition to this, humans live in association with many microorganisms present in the skin, mouth, genitourinary system, and gastrointestinal tract (GIT), known as the human microbiota (Mohajeri et al. 2018). The GIT contains the most numerous and diverse microbial communities of the body (Ji et al. 2020; Yin et al. 2019). In recent years, there has been a breakthrough in the knowledge of the human microbiota. It has been seen as necessary to maintain an adequate state of health since it interacts and causes changes in a multitude of tissues and organ systems, energy metabolism, as well as acts both in the immune system development and in the regulation of its responses (Gomaa 2020). The microbiome is influenced by several factors from the moment of pregnancy, the delivery type (i.e, vaginal and cesarian), the feeding of newborns, the geographical location, pollution, diet and lifestyle (Goertz et al. 2019; Selma-Royo et al. 2021; Su and Liu 2021). Thus, its alteration in composition and functioning leads to the appearance of metabolic disorders relevant to the development and perpetuation of chronic diseases (Ji et al. 2020).

Even though the positive effect of several dietary compounds on the composition of gut microbes has been already shown, a comprehensive evaluation is still necessary to study the impact of health-promoting bioactives (e.g., polyphenols, carotenoids, glucosinolates, vitamins, etc.) on the composition of microbial communities and their subsequent impact on health status. These bio-functional compounds present in various food sources improve host health by regulating the composition and configuration of the

gut microbiota (GM). Therefore, they modulate the GM and are new bio-safe strategies to control and reduce intestinal oxidative stress (OS) (Carrera-Quintanar et al. 2018; Ji et al. 2020; Rajoka et al. 2021; Yin et al. 2019). Recently, researchers have observed how supplementation with some bioactive molecules, such as carotenoids, is beneficial in improving the composition and diversity of the GM and, in turn, in contributing to reducing the risk of diseases caused by dysbiosis and/or alteration in the composition, amount or function of the microbiota (Lyu et al. 2018; Maoka 2020; Wiese et al. 2019). Thus, there is a growing interest in research regarding the relationships between GM and diet, particularly the production of numerous small molecules after colonic fermentation and GM-associated metabolites.

The present review will address some of the key issues such as the influence of diet on the microbiota and the potential beneficial effects of its bio-components in the prevention of the development of pathologies or the improvement of the state of the intestinal microbiota. For that purpose, one of the multiple variables that can affect the microbiota, as is the case of food, will be evaluated. This overview will focus on bioactive compounds, specifically carotenoid pigments, and their positive effects on the microbiota and their possible positive effect on disorders like dysbiosis by providing a greater microbiological diversity. Also, this review will include and discuss how the type of diet influences the microbiota, as well as the positive effects of gut bacteria and the microbiota after consuming a diet rich in carotenoids, which bacteria develop in the intestine after a high intake of the different types of carotenoids, and finally, possible health benefits derived from the increased intake of carotenoids on human health.

2. Methodology

The methodology given in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) has been employed for developing this review (Page et al. 2021). A systematic search was carried out to select articles published over two decades for compiling this review. The keywords used for the search of relevant articles were “carotenoids”, “gut”, “gut microbiota”, “dietary phytochemicals”, “human health”, “gut fermentation”, “intestinal microbiota”, “digestibility”, “antioxidant” and along with the Boolean operators AND, OR and NOT “plant sources”, and “nutritional quality”. Scopus, PubMed, Google Scholar, and Web of Science databases were accurately searched to achieve the desired results. All the articles were analysed and read carefully, and the articles which do not contain the desired information about carotenoids and GM were

removed. After a systematic review of the carefully chosen literature, the results of the authors were compared and considered until a consensus was reached.

3. Gut microbiota

GM consists of 100 billion microorganisms that reside in the human intestines, compared to the 30 billion human cells that the human body contains (Sender, Fuchs, and Milo 2016; Thursby and Juge 2017). In addition, the colonization and spatial organization of the GM are not uniform throughout the GIT (Dan et al. 2022; Kho and Lal 2018; Kilian et al. 2016). Over 90% of bacteria are divided into four families of *Bacteroides, Firmicutes, Proteobacteria*, and *Actinobacteria*, although *Fusobacteria* and *Verrucomicrobia* can also be found (Rinninella et al. 2019; Thursby and Juge 2017).

Humans have a high concentration and great microbial diversity in the skin, mucous membranes, and GIT. Therefore, it is of great interest and utility to increase the number of beneficial commensal microorganisms as a promising strategy to promote health (LeBlanc et al. 2013; L. Lin and Zhang 2017; Louis, Hold, and Flint 2014; Morrison and Preston 2016). The GM can be considered a metabolic organ since it is in constant communication with many of the body systems (e.g., the endocrine or immune system). This communication is established through metabolites produced by the GM that spread through the blood system throughout the body (Patrice D. Cani and Knauf 2016; Zheng, Liwinski, and Elinav 2020). As well, it has an important role in human health due to its ability to offer protective, immunological, and metabolic functions. Therefore, any change in its composition ultimately affects the health of the host, being unique to each person (Conlon and Bird 2015; D. Li et al. 2019; Rinninella et al. 2019).

The absence of diversity in the gut microbial community can lead to dysbiosis and imbalance in the microorganisms affecting genetically susceptible people, promoting adiposity, insulin resistance, dyslipidemia, or an inflammatory phenotype. Dysbiosis can be induced by various factors, including diet, place of residence, lifestyle, environment, use of antibiotics, chronic diseases, or genetic inheritance. Also, the manipulation of the GM with prebiotics, probiotics, vitamins, minerals, fermentable fibres, and polyphenols, could selectively stimulate the growth of beneficial bacteria helping to maintain a healthy intestinal environment or improve the unhealthy status of patients (Markowiak and Ślizewska 2017; Vieira, Fukumori, and Ferreira 2016) (**Figure 1**).

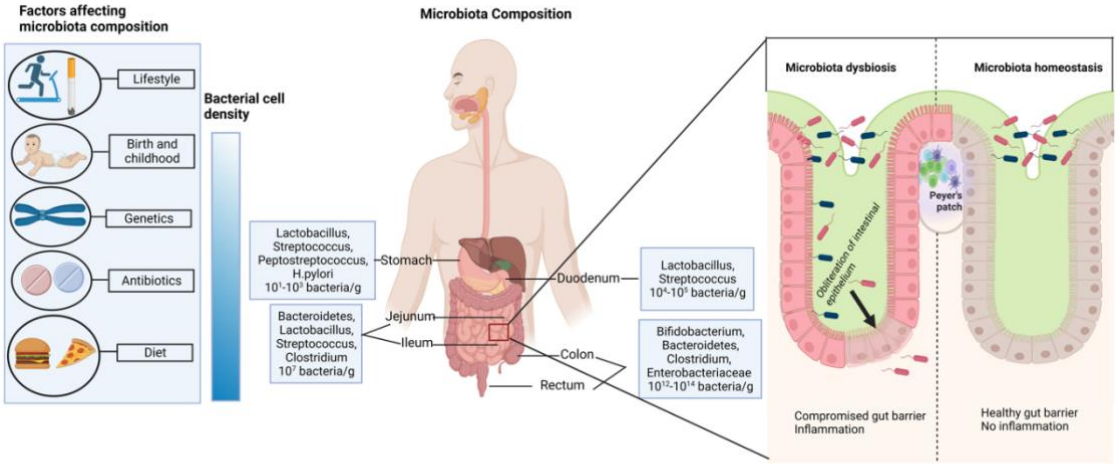


Figure 1. Distribution of the human microbiota along the intestinal tract, external and intrinsic factors that affect its composition and microbiota dysbiosis. The concentration of bacteria increases along the GIT.

As a result of disbyosis, intestinal homeostasis may be lost and produced inflammatory bowel, neurological, CVD, diabetes, and obesity diseases (P. D. Cani et al. 2007; Fu et al. 2021). Also, this can occur by oxidative injury when the antioxidant system is unable to remove additional reactive oxygen species (ROS) generated in the host body. Oxidative stress mainly damages macromolecules such as nucleic acids, proteins, and lipids, which can ultimately lead to intestinal diseases (Cooke et al. 2003; Pizzino et al. 2017). Antioxidant substances can inhibit OS mediated by free radicals, as well as their toxic effect on the host organism (Jiang 2014; Valdecantos et al. 2010).

In addition to the foregoing, the microbiota is involved in important host functions, at a physiological and metabolic level. The ability to ferment undigested foods and the participation in the metabolism of carbohydrates and proteins can render metabolism products such as vitamins and short-chain fatty acids (SCFAs; butyrate, acetate, and propionate), which can act as important substances with regulatory and energetic functions in intestinal epithelial cells (de Vadder et al. 2014; Guarner and Malagelada 2003). The metabolism-related products can strengthen the mucosal barrier, induce the production of anti-inflammatory molecules, prevent colorectal cancer (CRC), and the proliferation of antitumor cells by creating a protective barrier in the intestinal mucosa (Fang et al. 2021).

Butyrate, as the main source of energy for colonocytes, is responsible for the regulation of cell proliferation, differentiation, and apoptosis. Acetate influences the hypothalamus which reduces appetite, while propionate metabolized in the liver decreases liver lipogenesis and serum cholesterol levels (Louis and Flint 2017; Morrison and Preston 2016). Likewise, the catabolism of proteins and lipids exerts a significant impact on the GM composition which, in turn, influences the physiological state. Moreover, microbiota plays a great role in immune system development by influencing the physiology and gene expression of various cells in the host's body (W. K. Kim et al. 2019; Petit et al. 2022).

The interaction between the microbiota and immune cells promotes the creation of various signals facilitating the differentiation of immune cells, the maturation of the immune organ, and the development of other immune functions, such as the improvement of the phagocytic activity of macrophages, the generation of antibodies and the differentiation of T cells (Luu et al. 2018). Additionally, maintaining the integrity of epithelial cells, avoiding damage to the epithelium, the entry of harmful and toxic substances, as well as the connection from cell to cell, ultimately lead to the restoration of enterocytes and damaged epithelial cells (Dzidic et al. 2018; Gensollen et al. 2016).

4. Variation in the composition of the intestinal microbiota according to diet

Studies showed that diets can quickly alter the composition of the human GM, but if the diet is not prolonged, the composition of the GM returns to its original values within a few days. An effective change in the composition of GM requires persistent dietary habits. Therefore, it is necessary to uniquely examine each type of bioactive substance and to know what modulations it creates in the microbiota through its digestion and production of intestinal bacteria (David et al. 2014). Physiological aspects of the intestinal environment can be influenced by diet-related mechanisms including the absorption of micronutrients, vitamins, and nutraceuticals, as well as changes in the pH of the intestinal environment, which in turn alters the balance of the intestine (Carrera-Quintanar et al. 2018; Rajoka et al. 2021).

Diets rich in carbohydrates and simple sugars result in the proliferation of *Firmicutes* and *Proteobacteria*, whereas those rich in saturated fats and animal-derived proteins favour *Bacteroidetes* and *Actinobacteria* (Eid et al. 2017; G. D. Wu et al. 2011). In the study of Tilg, Moschen, and Kaser (2009), the authors described that gut microbiota changes due to the alteration from a diet rich in carbohydrates, but low in fat, to a high carbohydrate/fat diet. The proportion of *Bacteroidetes* species decreases, while the

presence of *Firmicutes* first increases and then prevails. The study carried out by de Filippo et al. (2010) found differences in gut microbiota population comparing faecal samples of African children, whose diet was hypocaloric and rich in fibre, with those of Italian children whose diet was based on meat, animal fat, refined carbohydrates, and sweetened drinks. African children showed an increase in *Bacteroidetes* and depletion in *Firmicutes* and *Enterobacteriaceae* were significantly underrepresented compared with EU children. In addition, significantly more short-chain fatty acids in African than in EU children were found.

Proteins and lipids are digested and assimilated effectively in the small intestine. However, if the diet is very rich in fats and proteins, part of these macromolecules may reach the colon and be processed there, with undesirable consequences (D. Li et al. 2019). Some studies have shown that consumption of a high-fat diet reduces the abundance of *Eubacterium rectale, Clostridium coccoides*, *Bifidobacterium*, and *Bacteroides* (P. D. Cani et al. 2007). Furthermore, diets rich in proteins and lipids tend to increase the incidence of gastrointestinal cancers, while polysaccharide-rich foods have the opposite effect (Conlon and Bird 2015).

Beneficial effects of high-added-value compounds on GM especially omega-3 polyunsaturated fatty acids (PUFAs) have been reported, which improve intestinal homeostasis and influence metabolic dysfunction. The consumption of PUFAs plays a pivotal role in the adhesion of the GM to the mucosal surface and the growth of intestinal bacteria (Fu et al. 2021; Kankaanpää et al. 2001).

Most *Bacteroidetes* are found in a diet of vegetable origin since they can use the resistant starch and oligosaccharides present in the prebiotic fibers (e.g., inulin and galactooligosaccharides (GOS)) as they are not digested in the small intestine. However, most *Firmicutes* are present in diets based on animal fats and refined carbohydrates, as they do not have the machinery to digest complex carbohydrates and prefer macronutrients of animal origin, including saturated fatty acids and proteins (Tilg, Moschen, and Kaser 2009). Although consuming a high-fibre diet reduces the population of *Lactobacilli* and *Porphyromonadaceae*, it increases the abundance of *Lachnospiraceae, Bifidobacterium*, and *Prevotellaceae* (Hashemi et al. 2017). In addition to changing the microbiota composition, consuming a high-fibre diet improves SCFA production, insulin secretion, and glucose tolerance, whereas it reduces weight gain and endogenous glucose production. For example, the traditional Mediterranean diet, as a successful dietary model, protects the host's body against CVDs. It is characterized by the

consumption of a high proportion of vegetables and a low proportion of meat and its products. Good dietary intervention is associated with benefits in the microbiota and an improvement in the microbial diversity of patients, which could alleviate dysbiosis-causing metabolic diseases (Nagpal et al. 2019).

Conversely, processed foods typically contain additives, artificial flavourings, preservatives, emulsifiers, antibiotics, or contaminants, such as organic contaminants, heavy metals, pesticides, and herbicides that have harmful effects on GM. Persistent consumption of foods containing antibiotics alters the microbiota composition in adults, leading to a significant decrease in microbial diversity and an increase in antibiotic resistance (Medina-Reyes et al. 2020; Patangia et al. 2022).

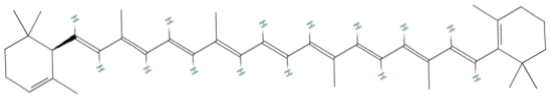
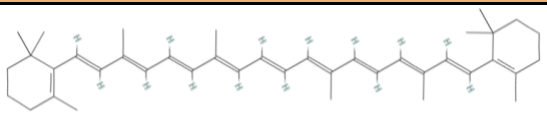
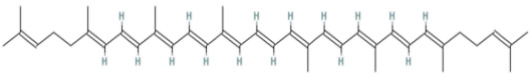
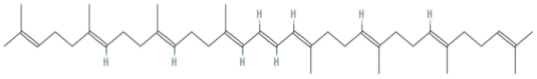
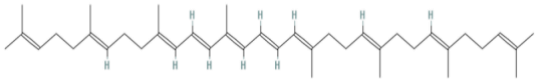
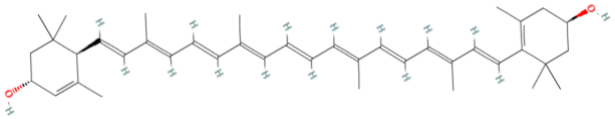
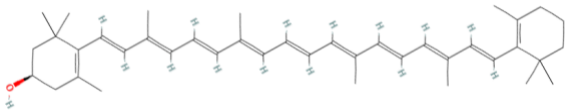
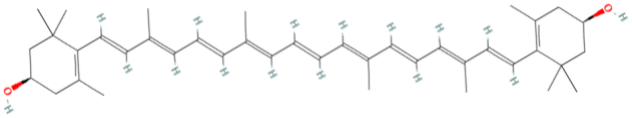
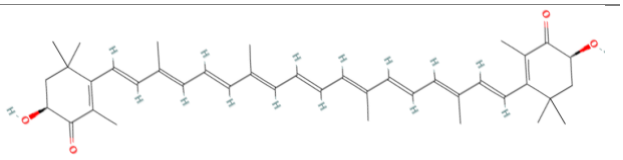
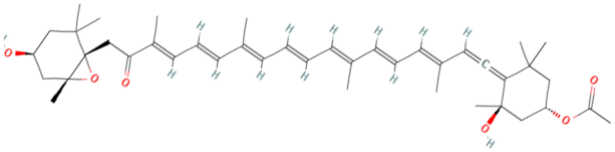
In addition, the age of the host must be considered as one of the key factors. Age can affect the number of interactions between nutrients, microbiota count, and health status (Bartley et al. 2017; Pellanda, Ghosh, and O'Toole 2021). For instance, the high consumption of monounsaturated fatty acids (MUFAs) has been correlated with higher levels of serum pro-inflammatory cytokines, while that of PUFAs showed a negative correlation with them, in elderly individuals. However, such associations in middle-aged people were not observed. Some studies have revealed a significant positive association between fibre consumption and the production of SCFAs, and between insoluble fibre and butyric acid levels in the elderly, suggesting consideration of the diet of the elderly for the promotion of an adequate microbiota to favour health status and prevent dysbiosis (Salazar et al. 2019).

5. Bioactive compounds: Carotenoids

Carotenoids are a class of naturally occurring fat-soluble pigments biosynthesized by plants, algae, cyanobacteria and some non-photosynthetic bacteria, fungi and arthropods. They are isoprenoids widely distributed in foods. A difference of carotenoids with other bioactives is that some carotenoids can be converted into vitamin A, which is an essential nutrient for humans. They can be classified into two main groups depending on the presence or absence of oxygen in their molecule's carotenes (which are hydrocarbons e.g., α-carotene, β-carotene, and lycopene) and xanthophylls (which are oxygenated e.g., astaxanthin, lutein, zeaxanthin, and β-cryptoxanthin) (**Table 1**). Carotenoids can be cleaved into apocarotenoids and other derivatives through non-specific reactions (via singlet oxygen, lipoxygenase cooxidation or photooxidation) or enzymatically, as a result

of which a myriad of compounds that are attracting increase interest in agri-food and health are obtained (Rodriguez-Concepcion et al. 2018; Mapelli-Brahm et al., 2020).

Table 1. Chemical structure of carotenoid types. Carotenes are indicated in orange and xanthophylls are colored in yellow. Structures were obtained from National Center for Biotechnology Information (2022). PubChem Compound Summary. Retrieved December 12, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/.

Carotenes	
	
α-Carotene	β-Carotene
	
Lycopene	Phytoene
	
Phytofluene	
Xanthophylls	
	
Lutein	β-Cryptoxanthin
	
Zeaxanthin	Astaxanthin
	
Fucoxanthin	

About 40-50 carotenoids are present in a typical human diet whilst ~20 carotenoids have been identified in human blood and tissues (Iddir et al. 2020). Humans and most animals cannot synthesize carotenoids *de novo*, and they obtain these coloured compounds through the foods they eat. Through dietary consumption, carotenoids are absorbed and deposited in the tissues (**Maoka, 2020**). Overall, the main dietary sources of carotenoids are fruits and vegetables. They can also be obtained from cereals, herbs, legumes and oils (***Dias et al., 2018; Dias et al., 2021; Gavahian et al., 201***9) and animal foods (including dairy products, egg yolks, fish, shellfish, etc.). Emerging potentially sustainable sources are algae, fungi, bactéria and even insects **(Meléndez-Martínez et al., 2021**). Some major dietary foods for the main carotenoids in humans are shown in **Table 2**. The carotenoid levels can vary greatly as a result of genetic, agronomic and climatic factors, among others such as industrial and culinary treatments (Dias et al. 2018; Dias et al. 2021; Antonio J. Meléndez-Martínez 2019). Carotenoids can also be obtained as food colour additives (from meat derivatives, soft drinks, sauces, confectionery, dairy, etc.) or from supplements(Meléndez-Martínez et al., 2019). Carotenoids are released from the food matrix in the mouth and begin their journey through the gastrointestinal tract (GIT). They undergo several changes through the stomach and intestines, including being solubilized by intestinal secretions. The gut flora uses non-bioaccessible substances, whereas the bioactive substances in the intestine are chosen through permeation and made available for absorption into the bloodstream (Reboul, 2019). After consuming them, these carotenoids follow an absorption mechanism that can be seen in Figure **2**.

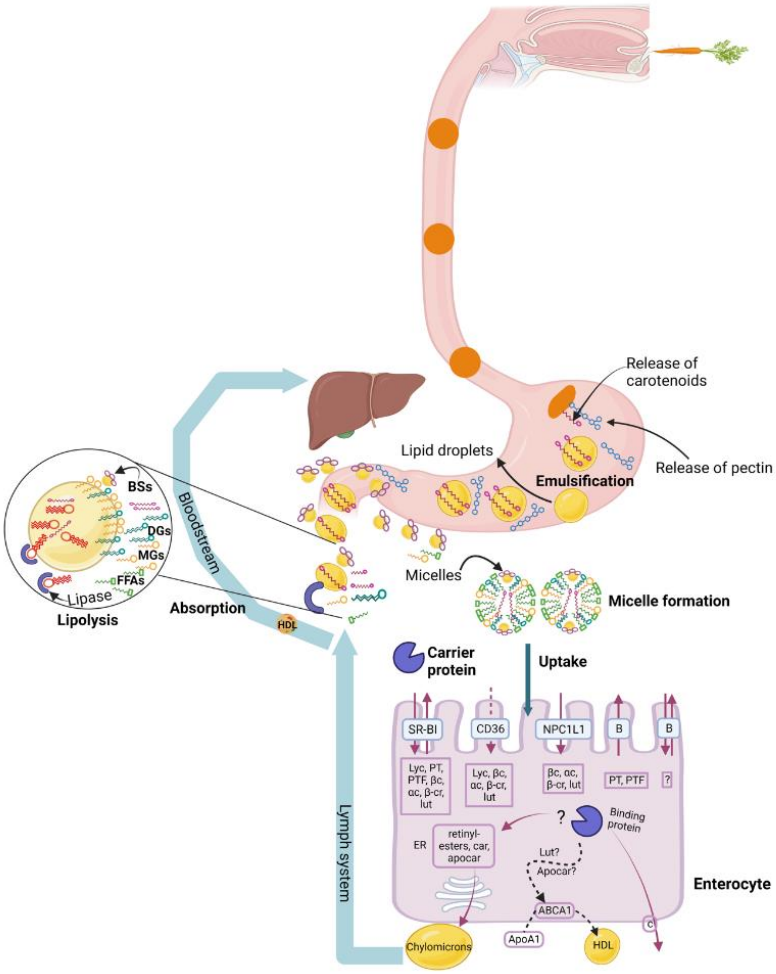


Figure 2. Mechanism of carotenoid absorption through GIT. The phases of lipolysis, emulsification, micelle formation and absorption into the bloodstream are shown.

Traditionally, lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene and lycopene have been considered the main food carotenoids bioavailable in humans, although there is now compelling evidence that the largely ignored colourless carotenoids phytoene and phytofluene are major dietary carotenoids and are also readily bioavailable and found in human fluids and tissues (Antonio J. Meléndez-Martínez and Mapelli-Brahm 2021). The presence of carotenoid cleavage derivatives (usually termed apocarotenoids) has also been demonstrated in foods and humans (Kopec et al. 2015; Schaub et al. 2017). Apocarotenoids are attracting increasing interest as they may be involved in the health-promoting biological actions attributed to carotenoids (Antonio J. Meléndez-Martínez 2019).

Table 2. Main food sources of carotenoids. Carotenes are indicated in orange and xanthophylls are colored in yellow. Data collected from (Dias et al. 2018; Dias et al. 2021; Din et al. 2022; Antonio J. Meléndez-Martínez 2019; Villaró et al. 2021).

Carotenoid type	Main plant sources
α-Carotene	Palm oil, carrots
β-Carotene	Orange carrots, palm oil, gac oil, buriti, mango, orange sweet potato, apricot, green vegetables
Lycopene	Watermelon, tomatoes, pink grapefruit, red papaya, red guava, sarsaparrilla
Phytoene	Tomatoes, apricots, red peppers, carrots, red grapefruits, oranges
Phytofluene	Tomatoes, apricots, red peppers, carrots, red grapefruits, oranges
β-Cryptoxanthin	Mandarin, red pepper, papaya, persimmon, pitanga, tangerines
Lutein	Sastra, green vegetables, egg yolk, pumpkin, sea buckthorn, marigold flower
Zeaxanthin	Sastra, corozo, sapote, quince, orange pepper, red pepper, Chinese wolfberry, buriti, sea buckthorn, marigold flower
Astaxanthin	Sockeye salmon, red trout, lobster, shrimp, crawfish, crab, salmon roe, and red sea bream
Fucoxanthin	Brown seaweed

The individual intakes of the major carotenoids, including phytoene and phytofluene, in humans are usually found in the interval 0-5 mg/day, although that of β-carotene and lycopene has been reported to be higher in some studies (Biehler et al. 2012; Antonio J. Meléndez-Martínez et al. 2022; Olmedilla-Alonso et al. 2021). Other carotenoids such as fucoxanthin, astaxanthin and canthaxanthin are usually obtained from marine food or supplements (Antonio J. Meléndez-Martínez 2019; Antonio J. Meléndez-Martínez et al. 2022). However, the bioavailability of carotenoids is far from complete, which means that a large proportion of the ingested carotenoids is not absorbed and can interact with the gut microbiota. A recent comprehensive review reported that it is unknown to what extent the microbiota contributes to carotenoids' bioavailability and metabolism as it is known that only 5-50 % of carotenoids are absorbed in the small gut, and only 10–50%

of the carotenoids remain intact after colonic fermentation, while the remainder reacts to unidentified compounds (Bohn et al. 2017).

On the other hand, evidence has been provided that carotenoids uptake by the enterocytes can be effluxed to the gut lumen (Paula Mapelli-Brahm et al. 2018). The biological roles of carotenoid oxygenases in bacteria is mostly unknown. However, there is evidence that they catalyze the formation of apocarotenoids that act as photoprotective and accessory pigments in cyanobacteria and that they also catalyze the formation of retinal or similar compounds in some archaea and eubacteria (Ahrazem et al. 2016). Besides, evidence that the colonic microbiota can maximize the bioaccessibility of carotenoids by the digestion of plant cell walls has been reported. These results are consistent with the significant role of colonic microbiota in the accessibility of specific carotenoid from fruits and vegetables in humans (Djuric et al. 2018). Thus, important fractions of carotenoids appear in the faeces of humans, as recently shown in a baby fed different vegetable-containing purees and 101 healthy adults (Rodríguez-rodríguez et al. 2020) (Stinco et al. 2019). In general, the bioavailability of carotenoids is low especially when the foods are not processed as the bioavailability can be increased by technological treatments (heating, high pressure, milling, etc.) and culinary practices. As an example, high pressure has been shown to increase ~ 5-fold the bioaccessibility (potential bioavailability) of carotenoids with diverse chemical structures in mandarin and orange juices (Sentandreu et al. 2020; Stinco et al. 2020). On the other hand, just the addition of 5% sunflower oil to tomato pulps and powders led to ~ 3 to 4-fold increases in the bioaccessibility of colourless carotenoids (P. Mapelli-Brahm, Stinco, and Meléndez-Martínez 2018).

Apart from the key role of provitamin A carotenoids in health and to combat vitamin A deficiency, there is evidence from studies of different nature (*in vitro*, *in silico*, in animal models, epidemiological) that they can exert health-promoting actions leading to reduced risk or alleviation of diseases. For instance, cardiovascular disease, cancer (prostate, breast, cervical, ovarian, colorectal, gastric, oral, laryngeal), bone disorders, skin disorders, eye disorders, dementia or metabolic disorders. There may also be important during pregnancy and early life and are also eliciting renewed interest as nutricosmetics. Concerning mechanisms, it is common to attribute the health benefits of carotenoids to their role as antioxidants, although there may be others (prooxidant, modulation of signaling pathways, immunomodulation, enhancement of gap junctional intercellular communication, light absorption) that can result in other effects, for instance, anti-

inflammatory (Böhm 2012; Eggersdorfer and Wyss 2018; Harrison and Quadro 2018; A.J. Meléndez-Martínez et al. 2021; Saini et al. 2020; Shin et al. 2020; Tanprasertsuk et al. 2021). Dietary antioxidants could protect the host from intestinal oxidative stress and reactive oxygen species (ROS) through modulation of the composition of beneficial microbial species in the gut, protecting from dysbiosis. Multiple *in vitro* studies have shown that carotenoids like β-carotene, lycopene, and lutein can reduce ROS generation, which can contribute to inflammation. For instance, lycopene has been hailed as an effective substance for reducing ROS produced by environmental variables like smoke (**Di Tomo et al.,2012**). Lycopene also can affect redox-sensitive cellular targets, such as protein kinases, protein tyrosine phosphatases, MAPKs, and transcription factors. According to research, lycopene can counteract smoke's effects on the molecular pathways that control inflammation, cell growth, apoptosis, and enzymes that activate carcinogens at a concentration of 2 μM (**Han et al., 2019; Bouayed & Bohn,2010; Kaulmann & Bohn 2014**). Additionally, it has been discovered to prevent smoke-induced DNA adduct formation and smoke-induced insulin-like growth factor signaling. In another study, 2 μM of lycopene drastically decreased ROS levels in human monocytes (THP-1) by 60%. Similar to how lutein (20 μM) and β-carotene (20 μM) significantly reduced ROS levels in AGS cells after H_2O_2 stimulation (by 20% and 10%, respectively). Moreover, after *Helicobacter pylori* stimulation, β-carotene (10 and 20 M) dramatically reduced ROS generation in AGS cells (**Kaulmann & Bohn, 2014; Palozza et al., 2012; Simone et al., 2013**). Another example of phytochemicals with a preventive or modulatory effect on oxidative stress is lutein. Ozawa et al. suggest in their studies that lutein inhibits oxidative stress derived from inflammatory activation pathways, including those related to the expression of IL-6 and transcription factor 3 (STAT3). Moreover, numerous studies and reviews have established a correlation between lutein intake and a reduction in symptomatic manifestations of neurodegenerative diseases, obesity, liver-related disorders, as well as those associated with intestinal dysbiosis and digestive tract inflammation.(Ozawa, et al., 2012; Ahn and Kim, 2021).

Moreover, Carotenoids have been reported to intervene in intestinal immune homeostasis by regulating the production of immunoglobulin A (IgA) and preventing or delaying the development of dysbiosis (Schmidt et al. 2021). Moreover, the release of SCFAs in both faecal and intestinal contents was observed at higher levels of carotenoid-rich fruits and vegetables (Carrera-Quintanar et al. 2018; Ji et al. 2020; Rajoka et al. 2021; Yin et al. 2019). In addition, they are thought to have various effects in the intestine and other

organs because greater consumption of carotenoids has been associated with a lower rate of overweight, prevention of obesity-related pathologies, contribution to maintaining the integrity of the intestinal mucosa and a more diverse microbial composition (Hegde et al. 2022). Serum carotenoid level has been shown to be inversely correlated with impaired intestinal barrier function, so supplementation could benefit its barrier function, immune homeostasis, and dysbacteria by accelerating the production of immunoglobulin A (IgA) in the gut (Ji et al. 2020). Some of the beneficial effects of carotenoids on health are summarized in **Table 3.**

Table 3. Some of the possible positive effects of different types of carotenoids on the human body. Carotenes are indicated in orange and xanthophylls are colored in yellow.

Carotenoid type	**Type of studies performed**	**Main findings** [a]
α-Carotene	Human clinical trials	▪ High levels of plasma α-carotene were associated with higher scores for global cognition, and episodic and semantic memory (X. Liu et al. 2021).
	Human cell cultures and rodents	▪ Inhibition of metastasis in Lewis lung carcinoma cell cultures and suppression of lung metastasis and tumor growth (combined with taxol) in tumor xenografted mice (Liu et al., 2023)
β-carotene	*In vivo* and *in vitro* tests	▪ β-carotene treatment may protect the impairment of oxidative stress and ameliorate MTX-induced intestine damage at biochemical and histological levels β-carotene have primarily antioxidant effects on lipids under stress but do not significantly affect the regulation of p53 gene expression (Wawrzyniak et al. 2013)
	Study on rodents	▪ Reduction of adiposity via the carotenoid cleavage oxygenases BCMO1 (Amengual, et al., 2011)
	Human clinical trials	▪ Positive effect of long-term supplementation of β-carotene (50 mg every other day) on cognitive function in men. (Grodstein, et al., 2007). ▪ Skin health benefits and treatment of erythropoietic protoporphyria (Zerres, & Stahl, 2020).

Lycopene	Human blood studies, *in vivo* and *in vitro* tests	▪ The main activity profile of lycopene includes antihypertensive, antiplatelet, anti-apoptotic, and protective endothelial effects (Mozos et al. 2018). ▪ Anti-prostate cancer activity(Moran et al., 2022). ▪ Possible positive effect on the risk reduction of cardiovascular disease (Bohm, 2012). ▪ It had anti-inflammatory effect on liver and impact on lipid metabolism (Fenni et al. 2017) ▪ Low serum lycopene was associated with early atherosclerosis, as manifested as an increased thickness of the common carotid artery (O. Y. Kim et al. 2010) ▪ Skin health benefits (Zerres, & Stahl, 2020)
Phytoene		▪ It may contribute to the health-promoting biological actions attributed to lycopene in studies with tomato products (Meléndez-Martínez, et al., 2019). ▪ Skin health benefits including possible anticancer activity (Meléndez-Martínez, et al., 2019) ▪ Phytoene and phytofluene levels in adipose tissue inversely correlated with diastolic blood pressure. Inverse relationships between total body fat content and central fat and most of the carotenoids detected in serum, including phytoene and phytofluene (Harari et al., 2020) Anticancer activity in breast and endometrial hormone-dependent cancer cells treated with either 17b- estradiol or genistein (Hirsch, et al., 2007)
Phytofluene	*In vitro* tests	▪ Anti-prostate cancer effect in PC-3, DU 145 and LNCaP human prostate cancer cell lines and rodent model (Kotake-Nara, et al., 2001; Campbell et al., 2006) ▪ It may contribute to the health-promoting biological actions attributed to lycopene in studies with tomato products (Meléndez-Martínez, et al., 2019) ▪ Phytoene and phytofluene levels in adipose tissue inversely correlated with diastolic blood pressure. Inverse relationships between total body fat content and central fat and most of the carotenoids detected in serum, including phytoene and phytofluene (Harari et al., 2020) ▪ Anticancer activity in breast and endometrial hormone-dependent cancer cells treated with either 17b- estradiol or genistein (Hirsch, et al., 2007)
β-cryptoxanthin		▪ Beneficial role in osteoporosis (Yamaguchi, 2008). ▪ Anti-lung cancer effect (Chiaverelli, et al.,2023)
Lutein	Human clinical trials, *in vivo* and *in vitro* tests	▪ High levels of lutein can be found in human breast milk. Infant brains improved neuronal development and cognitive function in the elderly (Schmidt et al. 2021). ▪ Beneficial effects on eye health and performance (Hammond, et al., 2014). Beneficial effects on cognition (Lindbergh, et al., 2018).

		▪ Lutein is suggested as being beneficial to cardiometabolic health because of its protective effect against oxidative stress (Leermakers et al. 2016).
Zeaxanthin	*In vivo* tests in mice and *in vitro* studies	▪ Beneficial effects on eye health and performance (Hammond et al., 2014) ▪ Beneficial effects on cognition ((Lindbergh, et al., 2018) ▪ Reduces weight and fat. Improves hypertrophy of adipocytes and decreases liver weight, dyslipidemia, leptin, glucose intolerance, and insulin resistance (Xie et al. 2021).
Astaxanthin	Human clinical trials, *in vivo* and *in vitro* tests	▪ Astaxanthin increased the production of IgA cells in the small intestine, being able to protect mucosal dysfunction during exercise. It activated T, B, and NK cells to produce IFN (Nagayama et al. 2014; J. S. Park et al. 2010). ▪ It has antioxidant and anti-inflammatory effects (Fakhri et al. 2018). ▪ Experimental investigations in a range of species using a cardiac ischaemia-reperfusion model demonstrated cardiac muscle preservation when astaxanthin is administered either orally or intravenously prior to the induction of ischaemia (Fassett and Coombes 2012). ▪ Disparate results in relation to effect on cardiovascular health and disease (Visioli, & Artaria 2017).
Fucoxanthin	Human clinical trials and *in vivo* tests	▪ Strong antioxidant and anti-inflammatory effect. Several animal studies showed that Fucoxanthin can prevent the development of chronic diseases, cancer, obesity, diabetes mellitus, and liver diseases (Bae et al. 2020). ▪ Clinical trials revealed that it reduces BMI, fatty areas, and waist circumference and thus has anti-obesity, antimetabolic syndrome, and antioxidant effects (Hitoe and Shimoda 2017).

[a] IgA: immunoglobulin A, NK: natural killer, IFN: interferon, BMI: body mass index, MTX: methotrexate

Carotenoids' Bioavailability and Accessibility

The bioavailability of carotenoids is defined as the highest quantity of carotenoids released from the food matrix that can be absorbed by the intestinal epithelial cells. It is known that the amount of a carotenoid that is consumed enters the bloodstream and has its physiological effects. Due to their resistance to digestion and degradation brought on by protein complexes and plant cell walls, carotenoids encounter difficulties regarding Bioavailability since these factors prevent their release from the dietary matrix. For instance, even though β-carotene has high activity and can be converted to vitamin A,

only about 65% of it is absorbed from plant sources, falling short of the advised 2-4 mg daily dosage(Fernández-García et al., 2012; Tanumihardjo et.al., 2010).

The Bioavailability and absorption of carotenoids are influenced by several variables, including dietary sources, food composition, cooking temperature, season, disturbance of the food matrix, presence of lipids, dosage, and other soluble compounds/carotenoids. These elements may increase carotenoids' Bioavailability, release them from the dietary matrix, or change them into isomers that the body may absorb more easily.

Carotenoids are released from the food matrix depending on their state; those completely immersed in lipid droplets are released more readily than those in microcrystalline form. Carotenoids are more bioavailable when ingested with a fat source than when consumed with dietary fibre like pectin (O'Conell et al., 2008). The cellular membrane can be damaged during thermal operations like cooking, boiling, and heating, which makes it easier for carotenoids to be released from the food matrix. Compared to raw food, these treatments increase Bioavailability and absorption even if they may lower the overall carotenoid concentration. For instance, cooked tomatoes are more lycopene-available than raw tomatoes, and the carotenoid content decreases with increased heat treatment. Therefore, the solubility and Bioavailability of carotenoids must be increased using various extraction processes. Hexane and acetone are examples of hydrophobic organic solvents used in conventional techniques. Carotenoids must first be purified using solvents approved for use due to their toxicity before being used in the food business.

Alternative carotenoid recovery techniques, such as supercritical fluid extraction (SFE), high hydrostatic pressure (HHP), and ohmic heating (OH), have been introduced in recent years. SFE lessens the need for harmful solvents but necessitates stabilizers and cosolvents, which may degrade or isomerize carotenoids. HHP improves the bioaccessibility of bioactive chemicals without the use of solvents (de Oliveira et al., 2020; Torres-Ossandón et al., 2018; Rocha et al., 2023)

6. Effect of major carotenoids on Gut Microbiota

In addition to the generic benefits that carotenoids can bring to human health, in recent years, many studies have evaluated the effect of the consumption of bioactive compounds on GM. However, the studies assessing the effect of carotenoid extracts or pure compounds are still limited. The efficiency of carotenoid activities appears to be significantly influenced by gut flora, according to several studies. Jalal et al. discovered that an overabundance of unfavorable bacteria, particularly Proteobacteria, resulted in

mucosal epithelial cell injury and increased intestinal permeability, which reduced carotenoid absorption. Studies employing colonic faeces samples showed that the gut microbiota produces new chemicals while fermenting carotenoids, demonstrating the metabolism of carotenoids. These findings show that although there is individual variability in carotenoid absorption, the composition of the gut microbiota has a major impact on carotenoid absorption and metabolism. (Kaulmann et al., 2016; Bohn et al., 2017).

Recently, using a 1,2 dimethylhydrazine (DHM) induced CRC mouse model, a significant increase in the abundance of *Firmicutes* and *Bacteroidetes* was observed upon supplementation with carotenoid-rich whole-cell lyophilized *Dunaliella salina* supplement (DSLP) as compared to the control DHM group (Gomathinayagam and Kodiveri Muthukaliannan 2021). Carotenoids may exert prebiotic effects, have been explored as adjuvants for inflammatory disorders and can increase microbial community and diversity, causing overall alterations (Hegde et al. 2022). Carotenoids are known to be cleaved by oxygenases by many organisms ranging from microbes to humans, hence it is feasible to think that gut microbiota could metabolize non-absorbed carotenoids in the gut (Bas-Bellver et al. 2020; Bohn et al. 2017; Rodriguez-Concepcion et al. 2018). The role of retinoic acid and carotenoids including pro-vitamin A carotenoids and xanthophylls in the maturation of the gut immune system and IgA production is being investigated (Lyu et al. 2018). On the other hand, carotenoid-producing cells of *Bacillus indicus* have been shown to provide beneficial effects in a rat model of diet-induced metabolic syndrome (Crescenzo et al. 2017). The effects of the main carotenoids on the microbiota are summarized in **Table 4** and reviewed below.

Table 4. Recent most relevant studies evaluating the impact of carotenoids on the Gut Microbiota. Carotenes are indicated in orange and xanthophylls are colored in yellow.

Sample	Type of study	Main findings [a]	Ref
b-carotene	Trial in female mice	It up-regulated the relative abundance of genera *Akkermansia*, *Candidatus Stoquefichus* and *Faecalibaculum*, but down-regulated the relative abundance of *Alloprevotella* and *Helicobacter*	Yang et al. 2021
	Experimental design with human gastric epithelial AGS cells	It inhibited H. *pylori*-induced hyper-proliferation of gastric epithelial cells by suppressing b-catenin signalling and oncogene expression.	D. Kim, Lim, and Kim 2019
Lycopene	Trial in male C57BL/6J mice	It decreased the relative abundance of *Proteobacteria* and increased the relative abundance of *Bifidobacterium* and *Lactobacillus*	Zhao et al. 2020
	Clinical trial in humans	It increased strains *Bifidobacterium adolescencia* and *B. longum* in the intestine along with an improvement in liver metabolism	Wiese et al. 2019
Astaxanthin	Trial in male C57BL/6 mice	It increased the levels of *Lactobacillus* and *Bifidobacteria*	L. Zhang et al. 2020
Fucoxanthin	Trial in male C57BL/6J mice	It inhibited inflammation-related *Lachnospiraceae* and *Erysipelotrichaceae* while increased the *Lactobacillus/Lactococcus*, *Bifidobacterium*, and some butyrate-producing bacteria	Sun et al. 2020
	Trial in BALB/c male mice	It modulated the ratio of *Firmicutes/Bacteroidetes* and the abundance of *Akkermansia*, thereby, it could be an auspicious microbiota-targeted functional food	Guo et al. 2019

[a] AR: adrenergic receptor, WAT: white adipose tissue

6.1 Effect of β-carotene on Gut Microbiota

β-carotene is a provitamin A carotenoid that can be found in high quantities in green vegetables, carrots, sweetpotatoes, mangoes and other dietary sources (**Table 2**). Alike lycopene, it is one of the carotenoids most studied in the context of health effects. Its key role as vitamin A precursor and therefore in combating vitamin A deficiency, one of the major nutritional problems in the world leading to high numbers of blindness and child

mortality, is indisputable. Besides, there is evidence that it can have beneficial actions in skin protection, fertility, immunomodulation and modulation of gene expressions. It has also been used therapeutically in the treatment of erythropoietic protoporphyria (Eggersdorfer and Wyss 2018; Antonio J. Meléndez-Martínez 2019). Dietary supplementation of β-carotene decreased the serum concentration of tumour necrosis factor-alpha (TNF-α) and IL-4 (cytokine involved in inflammation) in mice after delivery. Consumption of β-carotene improved intestinal integrity with a decrease in serum IL-4 concentration, which was negatively associated with the relative abundance of *Akkermansia*, a genus of microbes that have been reported to increase the number of goblet cells and barrier integrity. These results suggests that the decrease in IL-4 may be related to the occurrence of low-grade inflammation in normal pregnancy (Yang et al. 2021). Furthermore, it increased the relative abundance of the genus *Candidatus stoquefichus*, which was negatively correlated with the serum concentration of TNF-α and IL-4 in the study. It also enriched the genus *Faecalibacterium*, contributing to the production of butyrate along with a shift from lactate metabolism to the increased production of SCFAs as well as carbohydrate metabolism (Yang et al. 2021). Epidemiological studies have shown that a higher dietary intake of β-carotene reduces the risk of development and progression of many cancers including gastric cancer (GC). While the underlying mechanisms of tumor modulations include antioxidant effects, cell gap junction-related functions and immune-related functions affecting cell cycle progression, survival and immune surveillance, conclusive mechanisms of action are still unclear (Q. H. Chen et al. 2021). Some of the studies showed that β-carotene decreased DNA-dependent protein kinases Ku70 (70 kDa) expression *via* increased ROS generation (Y. Park et al. 2015), increased p53 expression and decreased anti-apoptotic protein Bcl2, ATM expression (Jang, Lim, and Kim 2009), and increased expression of p21WAF1/CIP1 and p53 expression (Z. M. Chen et al. 1999; Q. Wu, Chen, and Su 2001) in gastric cancer (GC). In addition, β-carotene by inhibiting lipid peroxidation and NF-kB inhibition prevent IL-8 production-mediated gastric inflammation (Y. Kim, Seo, and Kim 2011). Importantly, β-carotene by suppressing the β-catenin signaling pathway has been shown to prevent the *H. pylori-mediated* development of GCs (D. Kim, Lim, and Kim 2019). High-carotene diets have been reported to be beneficial for eye health and contribute to prevent macular degeneration (AMD). High serum levels of β-carotene were reported to reduce the risk of progressive AMD (L. Wu et al. 2020) and lung cancer (Cai et al. 2019). There is also evidence that the supplementation of β-carotene alleviates gut

microbial dysbiosis. R. Li et al. (2021) reported that β-carotene feeding supplementation decreases weaning-induced intestinal inflammation in pigs through changing gut flora that modulates growth, intestinal morphology, and inflammation. β-carotene feeding supplementation suppresses *Bacteroidetes, Prevotella* and *Blautia* species and enriches *Firmicutes, and Parabacteroides* species. *Prevotella* and *Blautia* are associated favorably with IL-1, IL-6, and TNF-α, while *Parabacteroides* are linked negatively suggesting that β-carotene mitigates the weaning-induced inflammation by altering the gut flora in pigs. Zhu et al. (2021) studied the effect of β-carotene on the gut microbiota community and its anti-inflammatory benefits in a rat model of ulcerative colitis induced by Dextran Sulphate Sodium (DSS). DSS treatment affected the phylum and genus abundance of gut microbiota and β-carotene therapy increased beneficial bacteria and reduces inflammatory cytokine levels. *Firmicutes* and *Actinobacteria* were less abundant in DSS than *Bacteroidetes* and *Proteobacteria* but β-carotene increased *Firmicutes* and *Actinobacteria* while suppressing *Bacteroidetes* and *Proteobacteria*. Furthermore, β-carotene could exert effects on the protection and prevention of intestinal diseases such as ulcerative colitis (UC), as it blocked the inflammatory factors in a rat model (Zhu et al. 2021).

6.2 Effect of lycopene products on Gut Microbiota

As commented above, lycopene (LYC) is one of the major dietary carotenoids found in humans. It is one of the carotenoids more extensively studied in relation to the biological actions of carotenoids. It is present in tomatoes, watermelon, red guava, red papaya, rose hips and sarsaparilla, among other sources (**Table 2**). Some of the possible health-promoting actions of lycopene are summarized in Table 3. Tomatoes and other lycopene-rich foods appear to protect against the harmful effects of UV rays. Several studies found that tomato paste consumption was linked to healthier skin after UV exposure than tomato product abstinence (Cooperstone et al. 2017; Stahl et al. 2001). Since tomato extracts or tomato products rather than pure lycopene have been used in many studies it is argued that other carotenoids present in tomatoes (for instance the colourless carotenoids phytoene and phytofluene) may be involved in some of the biological actions attributed to lycopene (Antonio J. Meléndez-Martínez and Mapelli-Brahm 2021).

The study conducted in DSS-induced colitis mice discovered a link between LYC consumption and gut microbiota population and metabolite production (Zhao et al. 2020). They administered lycopene (50 mg/kg body weight/day) in male mice for 40 days of therapy to realize its potential effect to prevent intestinal damage and inflammatory responses induced by DSS (Zhao et al. 2020). It was observed that lycopene attenuated the DSS-induced dysfunctions of anxiety- and depression-like behavior by suppressing synaptic damage, inhibiting neuroinflammation, and increasing expressions of neurotrophic factor and postsynaptic density protein, which may be closely related to the triggering effects on the GM, further relating to its gut-brain axis (GBA) (Luna and Foster 2015; Zhao et al. 2020). The study of Zhao et al. (2020) also showed how lycopene allowed the remodelling of the GM of mice. Initially, *Firmicutes, Actinobacteria*, and *TM7* were more abundant in the LYC group treatment group than in the DSS group, although *Proteobacteria* and *Deferribacteres* were more abundant in the DSS group. After lycopene consumption, mice with colitis reduce the relative abundance of *Proteobacteria* and raised the relative abundance of *Lactobacillus and Bifidobacterium.* Likewise, it was observed how lycopene stimulated the production of SCFAs in mice with colitis, avoiding the effects of inflammation produced by this disease, reversing endothelial deterioration, and its permeability. It was concluded that lycopene contributed to reducing behavioral disorders induced by DSS and colitis through the balance of the microbe-GBA, reducing the activation of brain microglia and inflammatory bowel/brain cytokines. In addition, lycopene also protected the brain against behavioral disorders by modulating the brain expression of brain-derived neurotrophic factor, as well as associated synaptic plasticity. Overall, previous studies indicated that lycopene could attenuate DSS-induced colitis, as well as associated anxiety and depression symptoms (Luna and Foster 2015). Therefore, it can also bring positive effects on the microbiota due to the relationship it has with lifestyle and emotional state. This may be due to the positive effects of lycopene in preserving the integrity of the intestinal barrier, as well as its modulatory functions on the microbiota and the associated production of metabolites (C. H. Lin et al. 2019; Zhao et al. 2020). Wiese et al. (2019) studied the effects of LYC and dark chocolate (DC) on gut microbiota, blood, liver metabolism, skeletal muscle tissue oxygenation, and skin in moderately obese people. Gut microbiota from faeces after four weeks of GA-LYC (GAL) supplementation showed a shift in the gut microbial population. GAL formulations increased the relative abundance of *Bifidobacterium spp*. and *Lactobacilli spp*. indicating prebiotic potential and continuous GAL, DC, and DCL

(DC+LYC) treatment reduced *Bacteroidetes* abundance either directly or indirectly by stimulating *Bifidobacteria* species.

As indicated in **Table 2**, tomato is one of the most relevant sources of lycopene. Xia et al. (2018) results suggest that tomato powder (TP) feeding increased the richness of the gut microbiome and microbial diversity in the HFD + DEN (Diethyl Nitrosamine, a liver-specific carcinogen) group in BCO1/BCO2 double KO mice, that is mice in which genes encoding for carotenoid cleavage oxygenases were knocked out. Gram-positive bacteria and Gram-negative bacteria co-exist in the gut and the overgrowth of Gram-negative bacteria enhances the production of hepatotoxic substances like LPS (Wigg et al. 2001). TP feeding supplementation boosted gram-positive bacteria and suppress Gram-negative bacteria, as they could verify when feeding with TP supplementation and the proportion of *Deferribacteres* decreased dramatically. This reduction, specifically from the genus *Mucispillirum*, may decrease the inflammatory cytokines. In the TP feeding group, *Clostridium sp. ID4* and *Clostridium sp. Clone.9* populations decreased and increased, respectively. *Clostridium* species have been found to increase hepatic lipogenesis and fat oxidation (Nadeau and Conjeevaram 2017). Lycopene could prevent intestinal damage and inflammatory responses in male mice induced by sodium dextran sulfate (DSS). Lycopene attenuated DSS-induced dysfunctions of anxiety- and depression-like behaviour by suppressing synaptic damage, inhibiting neuro-inflammation, and increasing expressions of neurotrophic factor and postsynaptic density protein (Riccio and Rossano 2018).

In conclusion, all these results show that lycopene causes a beneficial change in the microbiota both in the animals tested and in humans and directly or indirectly affects health.

6.3 Effect of Astaxanthin on Gut Microbiota

Astaxanthin (AsX) is a xanthophyll that is usually found in dietary fish (salmon, rainbow trout) and crustaceans, which together with zooplankton incorporate it from microbes, such as microalgae, yeasts, or bacteria. It is widely used as feed additive and dietary supplement, for which it is usually obtained by chemical synthesis or from the microalga *Haematococcus pluvialis*. This carotenoid has been the subject of many studies in relation to its possible health-promoting biological actions in relation to cancers, metabolic syndrome, diabetes, cardiovascular disease, and other disorders. There is evidence that astaxanthin could provide benefits at the level of the skin, which could be

important for cosmetic purposes (Davinelli, Nielsen, and Scapagnini 2018; A.J. Meléndez-Martínez, Stinco, and Mapelli-Brahm 2019; Yuan et al. 2011).

A recent study indicated that the supplementation of astaxanthin increased IgA levels, the production of IFN-γ, B cells and natural killer cells which may protect against immunity dysfunction. Thus, astaxanthin might confer beneficial effects by regulating the maturation of B cells and the production of IgA (J. S. Park et al. 2010). In the study carried out by L. Wu et al. (2020) it was observed that the use of astaxanthin led to changes in the microbiota, towards the suppression of the pathways of intestinal inflammation/OS by inhibiting the activation of the inflammation NLRP3 (NLR family pyrin domain containing 3) of the colon. It potentially attenuated the dysregulated neuronal pathways and modulated the regulation of intestinal inflammation/OS/apoptosis (L. Wu et al. 2020).

L. Zhang et al. (2020) studied cyclophosphamide-induced immune-deficient mice and found AsX treatment alters intestinal mucosa activity and changed the gut flora and metabolites. Results obtained highlight that β-carotene and AsX-treated (dose-60 mg/kg b.w.) groups had higher levels of *Lactobacillus* and *Bifidobacteria* and reduced *C. coccoide* and *Enterobacteriaceae spp*. Treatment of β-carotene and AsX increased total SCFAs. In immune-deficient mice, propionic acid and butyric acid levels usually dropped to 62% and 35%, respectively, but supplementation with β-carotene significantly increased these levels. AsX-treated animals had increased SCFA synthesis, especially acetic acid, propionic acid, and butyric acid, modulated intestinal immunity, reduced inflammation, and improved intestine function (L. Zhang et al. 2020). It was reported that an astaxanthin-containing supplementation shifted the overall structure of the gut microbiota in obese mice fed with a high-fat diet (HFD) toward that of normal chow-fed mice (Meng Wang et al. 2021).

In another study with mice infected with *H. pylori*, astaxanthin treatment could significantly low bacterial loads and attenuate gastric inflammation (Bennedsen et al. 1999). Also, the results obtained by (Nagayama et al. 2014) showed that astaxanthin supplementation significantly reduced the levels of inflammation and colonization and the number of IgA antibody-secreting cells (ASC) in mice's small intestines at weanling age. In conclusion, evidence has been provided that astaxanthin might have the potential to prevent or treat dysbiosis and its associated diseases.

6.4 Effect of Fucoxanthin on Gut Microbiota

Fucoxanthin (Fx) is an oxygen-containing carotenoid with an uncommon allenic bond, a 5,6-epoxide group, and a carbonyl group conjugated with the typical carotenoid polyene chain. Fucoxanthin is present in the diet of some groups of people as it occurs in edible brown algae such as *Undaria pinnatifida, Sargassum fusiforme,* and *Laminaria japonica* (H. Zhang et al. 2015). It is also a major carotenoid in microalgae such as *Phaeodactylum tricornutum* (Min Wang et al. 2022). Given the importance of brown algae in the diets of many South Asian populations, it is not surprising that the possible health-promoting biological actions of Fx has been the subject of many studies. Fx has been reported to exhibit *in vitro* and *in vivo* anti-inflammatory effects, suppress the cell cycle, induce apoptosis, prevent or reverse metabolic syndrome and have hepatoprotective, cardioprotective, and anti-diabetic effects in different types of studies (Fakhri et al. 2021). Other authors have reported that it might protect microglia and be beneficial in inflammatory diseases (Terasaki, Kubota, et al. 2021; Terasaki, Uehara, et al. 2021). Interestingly, intestinal bacteria can convert Fx to fucoxanthinol which leads to its bioavailability (Miyashita, Nishikawa, and Hosokawa 2018; H. Zhang et al. 2015). Fx has been shown in mice to have strong suppressive effects on colorectal, duodenal, and liver carcinogenesis but human interventional trials with Fx against cancer have yet to be conducted (Mikami and Hosokawa 2013). Guo et al. (2019) reported that *Nitzschia laevis* extracts (containing Fx) could attenuate HFD-induced obesity in mice by modulating gut microbiota composition. The Fx's anti-obesity activity was studied by evaluating microbial profiles of caecal and faecal samples from HFD-fed BALB/c mice and found major changes in *Firmicutes/Bacteroidetes* ratio, the abundance of the Bacteroidales family S24-7 and a promoting effect on the growth of *Akkermansia*. On this basis, it could be suggested that Fx can act regulating gut microbiota and might exhibit antiobesity effects. Terasaki, Uehara, et al. (2021) reported the possible chemoprotective efficacy of Fx. The results highlighted the impact on gut microbiota in a mouse model of inflammatory colorectal cancer upon administration of Fx (30 mg/kg BW) for 14 weeks, where Fx treatment decreased *Bacteroidales* and *Rikenellaceae* and increased *Lachnospiraceae*. Although more research is needed to elucidate the relationship between colorectal mucosal tissue and *Rikenellaceae* and/or *Lachnospiraceae* with the underlying molecular mechanisms. Oral treatment with a fecal suspension from Fx-treated animals increased *Lachnospiraceae* and suppressed colorectal adenocarcinomas and mucosal

crypts in Azoxymethane and Dextran sodium sulphate (AOM/DSS)-treated mice suggesting that an alteration in gut microbiota by dietary Fx could be a key factor to consider. The functional mechanisms of Fx's anticancer effects in vivo have been proposed to be anoikis induction and tumor microenvironment suppression. However, the precise anticancer mechanisms of Fx are not fully understood (Terasaki, Kubota, et al. 2021). These promising results suggest that Fx can be important in modulating the *Firmicutes*/*Bacteroidetes* ratio and *Akkermansia* abundance. Also, evidence of possible interaction with intestinal *Escherichia coli* and *Lactobacilli* towards inhibition of the growth of pathogenic bacteria has also been obtained (Z. Liu et al. 2019). In sum, Fx appears as a promising ingredient for products intended for microbiota modulation.

7. Safety of carotenoids

Carotenoids are very safe compounds naturally present in the diet of humans (from fruits and vegetables, cereals, herbs, legumes, oils, shellfish, fish, milk and dairy, egg yolk, algae, additives, supplements, etc.)) all over the world and in the mother's milk, the first food of infants [Dias et al., 2018; Dias et al., 2021; Gavahian et al., 2019)]. Two important factors that need to be taken into account when assessing carotenoid safety are intake and bioavailability. The maximum reported intakes of carotenoids in different countries is below 2.5 mg/day except in the case of β-carotene, lutein+zeaxanthin and lycopene, in which higher levels have been reported in some studies (8.80, 4.84 and 10.70 mg/day, respectively). Concerning, bioavailability, they have been reported in milk, semen, plasma (usually in the range 0 – 2 μmol/L) and in most tissues (usually in the range 0 – 1 nmol/g), although the so-called macular carotenoids lutein and zeaxanthin are much more concentrated in the macula lutea (Mapelli-Brahm, et al., 2020).

Two intervention studies (ATBC, CARET) involving individuals at high risk of developing lung cancer (current and previous heavy smokers, workers exposed to asbestos) concluded that supplementation with high doses of β-carotene over several years leads to an increase the incidence of lung cancer (Heinonen and Albanes, 1994). In other studies, in which high doses of β-carotene were supplemented to apparently healthy individuals, not detrimental effects or even lower mortality in some cases were observed (Kamangar et al., 2006; Grodstein et al., 2007). Among the reasons that can be added to explain the different results are differences in the volunteer's characteristics and habits (mainly exposure to lung carcinogens such as tobacco smoke or asbestos that can lead to

the formation of detrimental compounds), dosage, formulation of the supplements or plasma levels of β-carotene (Veeramachaneni and Wang, 2009). In any case, considering these studies the European Food Safety Authority (EFSA) concluded that "exposure to β-carotene from its use as a food additive and as a food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population, including heavy smokers"(EFSA, 2012). With this exception, the acceptable daily intakes of carotenoids authorized as food colours in the European Union are indicative of the wide margin of safety of carotenoids. For instance, the ADIs for major dietary carotenoids such as lutein or lycopene (1 and 0.5 mg/kg bw/day, respectively, that is 60 mg and 30 mg for a person of 60 kgs) exceed by far their daily intakes commented above.

8. Conclusions

Gut microbial communities may also play an important role in human health, not only at the intestinal level but at the systemic level. There is now evidence that carotenoids exert a prebiotic effect on the microbiota of the colon favouring the growth of certain species over others, such as *Lachnospiraceae, Bifidobacterium*, and *Prevotellaceae*. On the other hand, carotenoids are expected to be modified by the microbiota, giving rise to catabolites (apocarotenoids) that may exert relevant physiological effects. Very marked differences in the microbial composition of various individuals are also observed. These differences can affect the interaction of carotenoids with the GM, depending on the composition of available microbiota. In general, the consumption of certain foods rich in carotenoids/antioxidants can promote health.

Based on the reviewed studies, it is possible to conclude that supplementation with carotenoid-rich products is an interesting strategy that can contribute to prevent the development of colorectal cancer, intestinal pathologies, and states of inflammation, in addition to the protection of the intestinal epithelium against states of stress such as pathogens or possible intolerances. These health-promoting actions can be attributed to a certain extent to the development of beneficial intestinal bacteria such as *Akkermansia* and the formation of SCFAs to generate a greater diversity of intestinal microbes. In addition to other beneficial actions widely studied in the past, lycopene has been recently shown to stimulate the intestinal immune system and strengthen the intestinal barrier and its permeability. Among other beneficial actions, astaxanthin and fucoxanthin are thought to reduce the appearance of malignant tumours such as colon and rectal cancer, as well

as curb the incidence of CVDs derived from dyslipidemia, and states of digestive inflammation (such as obesity and metabolic syndrome).

According to recent studies, it appears that the modulation of gut microbiota can be considered another of the health-promoting actions carotenoids can contribute to. This fact opens new research possibilities in the carotenoid field. For instance, the study of the effect of dietary bioactive compounds such as carotenoids in intestinal bacteria closely related to the GBA is a timely research topic. The effects of carotenoid-rich algae (both microalgae and seaweeds), their carotenoids or even the effects of other common dietary carotenoids (lutein, zeaxanthin, β-cryptoxanthin, α-carotene, phytoene and phytofluene) also needs to be investigated. Furthermore, the production of apocarotenoids by the gut microbiota and the effects of such compounds require dedicated studies. Other aspects that need to be taken into account to gain further insight into the interaction of carotenoids with microbiota are bioavailability, dietary and other lifestyle habits, possible pathologies, genotype and even the influence of emotional state, rest, and physical activity, among others. Future research is warranted to elucidate more precisely the mechanisms by which carotenoids are preventive/protective in intestinal dysbiosis. This is important for the development carotenoid-based prebiotic products targeting GM.

Declarations

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Declaration of interest statement

The authors confirm that there are no known conflicts of interest associated with this publication.

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