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*Review Article*

# Impact of carotenoids on gut microbiome: Implications in human health and disease

**Pramukh Subrahmanya Hegde**
Nitte (Deemed to be University), KS Hegde Medical Academy (KSHEMA), Department of Physiology, Mangalore-575018 (Karnataka), India
**Megha Bhat Agni**
Nitte (Deemed to be University), KS Hegde Medical Academy (KSHEMA), Department of Physiology, Mangalore-575018 (Karnataka), India
**Praveen Rai**
Nitte (Deemed to be University), Nitte University Centre for Science Education and Research (NUCSER), Division of Infectious Diseases, Mangalore-575018 (Karnataka), India
**Mohana Kumar B**
Nitte (Deemed to be University), Nitte University Centre for Stem Cell Research and Regenerative Medicine (NUCSReM), Mangalore-575018 (Karnataka), India
**Damodara Gowda KM***
Nitte (Deemed to be University), KS Hegde Medical Academy (KSHEMA), Department of Physiology, Mangalore-575018 (Karnataka), India

*Corresponding Author. E-mail: dr_damodar@nitte.edu.in

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**Abstract**
Carotenoids are the colored compounds that prominently occur in fruits, vegetables, flowers, algae, fungi, yeast, and marine organisms. The coloration of carotenoids is mainly due to varieties of conjugated double bonds, which act as a light-absorbing chromophores. β-Carotene, α-Carotene, Lycopene, Astaxanthin, Lutein, Zeaxanthin, β-Cryptoxanthin, α-Cryptoxanthin, γ-Carotene and Fucoxanthin are the common carotenoids of the human diet. This review aimed at providing scientific evidence supporting the benefits of nutritional carotenoid intake on gut microbiota modulation in different disease models. Carotenoids have some beneficial effects on human health, and it is due to the activity of pro-vitamin A and antioxidant function. Although mechanisms are under investigation, studies suggest that carotenoid intake may reduce the risk of cancer, cardiovascular disease, eye disease, haematological disease, immune stimulants, and improve cognitive function. Recent studies have shown that carotenoids can modulate gut microbiota composition associated with host health. The human gut harbors a complex community of over 100 trillion microbial cells, influencing human physiology, metabolism, nutrition, and immune function. The combination of extrinsic (lifestyle and medication) and intrinsic (host genetics, immune and metabolic regulations) factors shapes the gut microbiota. Diet is a crucial modifiable factor influencing gut microbiota composition, indicating the potential for therapeutic dietary strategies to manipulate microbial diversity, design, and stability.

**Keywords:** Astaxanthin, β-carotene, Carotenoids, Fucoxanthin, Gut- microbiome, Gut dysbiosis, Human health, Lycopene.

## INTRODUCTION

"Carotenoids" are a collection of red, orange, and yellow-pigmented molecules that are synthesized by photosynthetic plants, algae, bacteria, and fungi. Around 700 specific carotenoids are identified in plant species and some species of algae and fungi. Carotenoid is a common term used to signify the non-nitrogenous biochromes, universally dispersed in residing entities in a lipophilic environment and is commonly insoluble in water (Zia-ul-haq *et al*., 2021).

Animals do not often produce carotenoids, although some animals (e.g., aphids) were proven to synthesize them *de novo*. Up to date, ~ 700 Carotenoids have been described, of which approximately 50 turn out to be components of the human diet, while only ~20 are found in human blood and tissues (Fiedor and Burda, 2014). The most important include β-Carotene, α-Carotene, Lycopene (LYC), Lutein, Zeaxanthin, β-Cryptoxanthin, α-Cryptoxanthin, γ-Carotene, Astaxan-

thin (AsX), Fucoxanthin (Fx), Neurosporene, ζ-Carotene, Phytofluene, and Phytoene.

**Structure and classification of carotenoids**

The International Union of Pure and Applied Chemistry (IUPAC) defines a carotenoid as a compound consisting of C-20 and C-20' intact methyl groups, with a structure characterized by the conjugated double-bond system that determines the colour (it acts as a light-absorbing chromophore). As the conjugated double-bond increases, colour varies from light yellow to orange to red. Traditionally, carotenoids are named according to their biological origin.

Carotenoids are classified into two categories according to the presence or absence of oxygen atoms in the molecule (Fig. 1). They are hydrocarbon Carotenes such as β-Carotene, α-Carotene, LYC, and oxygen-containing carotenoids, Xanthophylls, such as Lutein, Zeaxanthin, AsX, etc. Depending on chemical structure, carotenoids can be classified into cyclic carotenoids, acyclic carotenoids, hydroxy carotenoids (or Carotenols), epoxy-carotenoids, and uncommon or species-specific carotenoids. The molecular structure of carotene consists of only carbon and hydrogen and forms a polyunsaturated chain with the chemical formula $C_{40}H_{56}$ (Olatunde *et al*., 2020).

**Sources of dietary carotenoids**

Carotenoids are prominent in algae and photosynthetic bacteria as they can synthesize a variety of carotenoids, and are accumulated in cells called chromatophores (Table 1). Halobacteria (bacteria resistant to high salt concentrations) contains carotenoids in the form of β-carotene and forms a bright red blood cell suspension. Marine organisms, especially microalgae, have become the focus of identifying new biologically active natural substances in the last few years. In particular, it was reported that diatoms are one of the most promising microalgae groups, which possess a series of phytochemicals with beneficial biological activities. For example, the water extract of *Haslea ostrearia* shows antitumor and anti-proliferative effects, while the extract of *Chaetoceros calcitrans* shows antioxidant effects. Carotenoids are considered one of the main bioactive components in microalgae, however, studies have also shown that other compounds, such as polyphenols and polyunsaturated fatty acids, may impact their health (Galasso *et al*., 2017).

Microalgae contain many different types of carotenoids. Among them, about 30 species perform functions related to photosynthesis, while other species are intermediates for carotenoid production. Although many microalgae can produce carotenoids, only a few can accumulate sufficient carotenoids suitable for mass production. Only the unicellular green microalga *Haematococcus pluvialis* is cultivated on an industrial scale. These freshwater microalgae exist in temperate regions. Cysts can be formed under certain stress conditions, such as bright light, nitrogen deficiency, and high salt content and a large amount of AsX accumulated in the cytoplasm until the colour changes from green to greenish-red. For potential commercial cultivation*, Dunaliella salina* is another green microalga under study. It adapts to the extreme saline-alkaline conditions where very few organisms can survive and produce a large amount of β-Carotene to protect themselves from the intense penetration and light challenges (Galasso *et al*., 2017). In marine animals, sponges, sea urchins, krill shells and shrimps, and the scales of various fishes contain the highest amount of carotenoids. The pink to orange coloration of salmon and trout meat is also the result of carotenoid deposition, especially AsX, extracted from krill (Maoka *et al*., 2011).

Different fungi can produce and store high amounts of carotenoids in cells as microalgae. According to the reports, other species from the phyla *Chytridiomycota, Zygomycota*, *Chytridiales*, and *Basidiomycotina* have carotenogenesis capacity-like *Cantharellus sp*, *Phaffia rhodozyma*, *Blakeslea trispora* and *Rhodotorula rubra*. The mushroom *Cantharellus cinnabarinus* is one of the best examples of the naturally occurring orange-red oxygen-containing carotenoid Canthaxanthin. Another genus, *Rhodotorula* described as a natural source of β-carotene is of interest as a biological source, although its importance is minimal compared to other microorganisms (Echavarri *et al*., 2002).

Quantitatively, fruits and vegetables contain the maximum amount of natural carotenoids. Carotenoids are abundant in leaves, other green parts, flowers, roots, and seeds in terrestrial plants. Carotenoids in terrestrial plants mainly correspond to red and yellow xanthophylls, such as lutein, zeaxanthin, capsaicin, violaxanthin, or neoxanthin. In addition, marigold flower (*Tagetes standa*) and red pepper (*Capsicum annuum*) are good examples of the natural occurrence of yellow lutein, capsanthin, red xanthophylls, respectively. Many vegetables are rich in carotenes, such as LYC in tomatoes and β-carotene in carrots and sweet potatoes (Mezzomo and Ferreira, 2016).

In the stomach, the carotenoids are d emulsified into small lipid droplets (Fig. 2). From the lipid droplets, carotenoids are transferred to mixed micelles formed by the action of bile salts, biliary phospholipids, dietary lipids, and their hydrolysis products. The mixed micelles migrate to the brush border, where carotenoids are absorbed by the intestinal cells, packed into chylomicrons and secreted to the lymphatic system. The uptake of carotenoids from the intestinal lumen takes place by simple diffusion down a concentration gradient through the brush border membrane into the cytoplasm of the enterocytes mainly through carrier protein SR-BI.

The hairpin-like conformation of SR-BI external domain forms a hydrophobic channel that may facilitate the uptake of carotenoids by the enterocytes (Yonekura and Nagao, 2007).

**Dietary carotenoids and human health**

Carotenoids are not only colored pigments but also biologically active substances that positively affect human health (Fig. 3). β-carotene, cryptoxanthin, zeaxanthin, lutein, and LYC are common dietary carotenoids. This protective effect is due to the activity of provitamin-A and antioxidant function. Epidemiological studies have revealed that regular intake of carotenoids rich in fruits and vegetables reduces the risk of cancer, cardiovascular disease, eye disease, blood disease and enhances immunity (Yonekura and Nagao, 2007). The potential antioxidant properties of carotenoids can help prevent other diseases caused by free radicals. The oxidants produced during normal metabolism and immune defence against chemical substances and infectious pathogens are responsible for damaging DNA, proteins, and cells in the human body. This damage is considered the leading cause of aging and degenerative diseases such as cancer, cardiovascular disease, weakened immune system, and cataracts. The localization of carotenoid molecules in biological tissues also affects their ability to recognize and scavenge free radicals (Bakan *et al*., 2014).

**Carotenoids and gut microbiota**

The human gut harbours a complicated network of over a hundred trillion microbial cells that impact human physiology, metabolism, nutrition, and immune function (Guinane and Cotter, 2013). Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia, and Fusobacteria are the most common bacterial phyla observed in the human intestine (Rinninella *et al*., 2019). Gut microbiota (GM) diversity affects numerous metabolic and immune functions of the host's physiology. The GM is formed through a mixture of extrinsic elements (lifestyle and medication) and intrinsic elements like host genetics, immunity, and metabolic regulations. Diet is a crucial modifiable component influencing the composition of the GM, indicating the potential for therapeutic dietary strategies to manipulate microbial variety, composition, and stability. Consequently, an imbalance of GM or dysbiosis can be the reason for many pathological conditions like infectious diseases, gastrointestinal cancers, inflammatory bowel disorder, or even obesity and diabetes (Carrera-Quintanar *et al*., 2018).

Microbial dysbiosis indicates the depletion of beneficial microorganisms and the growth of potential pathogens (Feher *et al*., 2021). Therefore, GM is a suitable target for dietary interventions to boost health. Accordingly, carotenoids that may impact GM have recently been studied as adjuvants to remedy a few persistent and inflammatory diseases. Although the health benefits of carotenoids are well reported, only a small part of dietary carotenoids are absorbed from the intestine and eventually enter the body tissues. The rest enter the intestine and are metabolized by the microbiota (Bas-Bellver *et al*., 2020).

It has also been reported that carotenoids have potential prebiotic effects. Supplementation of carotenoids can increase the microbial community and diversity, leading to overall changes in the microbial community. Especially in humans, higher dietary carotenoids help inhibit many Firmicutes positively associated with overweight/obesity (Guo *et al*., 2019). However, there is a lack of information about the interaction between carotenoids and the GM. Based on the findings of recently

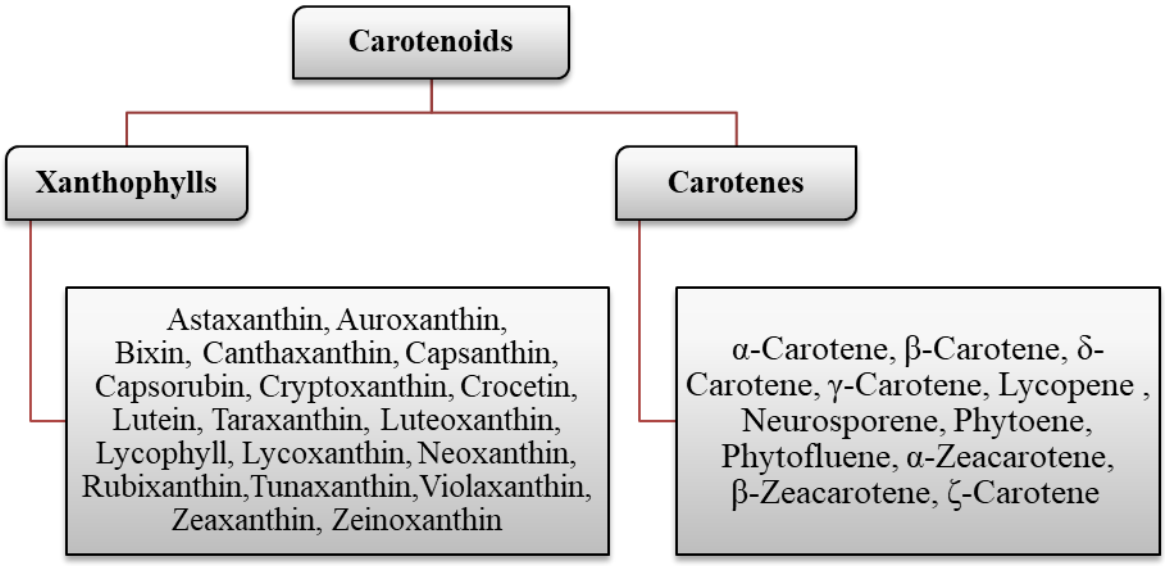



**Fig. 1.** *Classification of carotenoids depending on the presence or absence of oxygen in the molecule ( https:// www.tuscanydiet. net/2013/11/02/carotenoids-definition-structure-classification)*

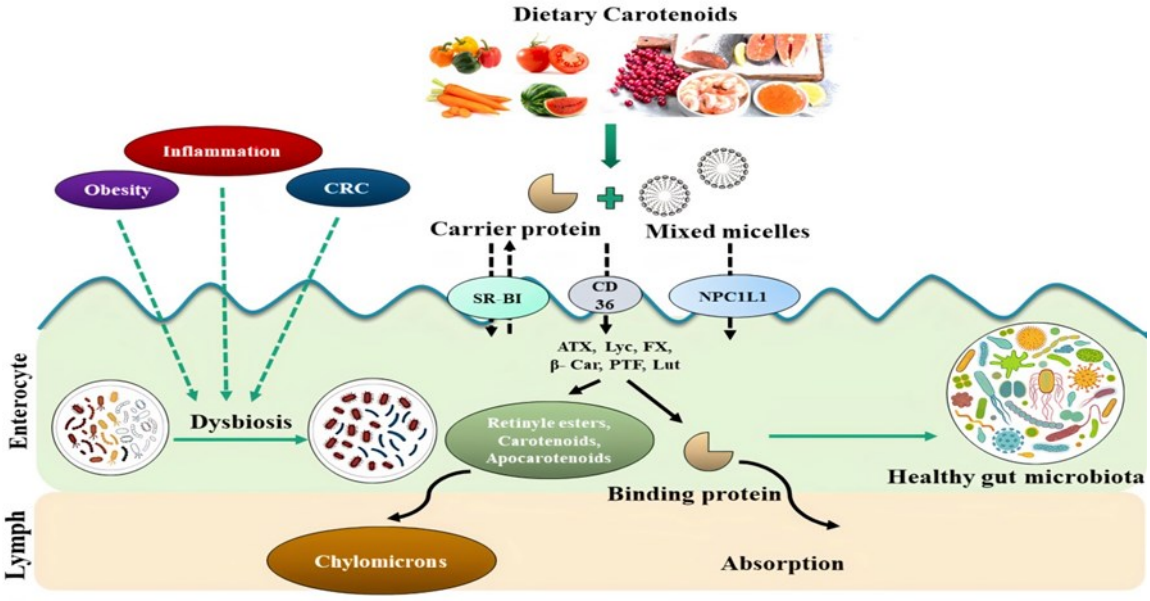



**Fig. 2.** *Absorption of dietary carotenoids and its role on gut dysbiosis (Source: Reboul et al., 2013)*

published studies, this review summarizes the interactions between intestinal flora and dietary carotenoids in the course of several disease conditions.

**Effect of astaxanthin on gut microbiota**

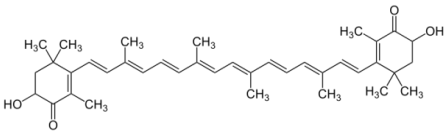
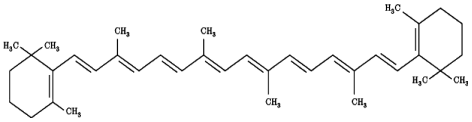
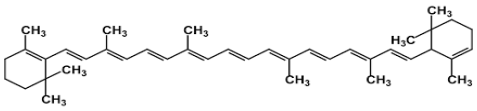
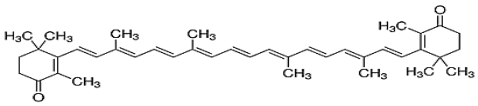
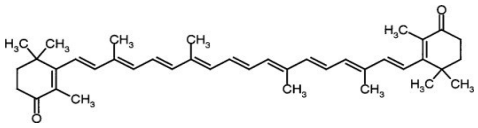
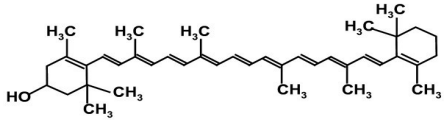
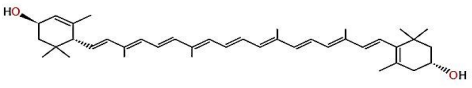
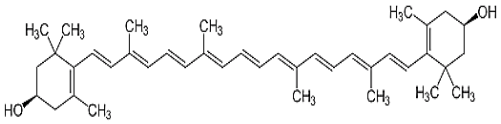
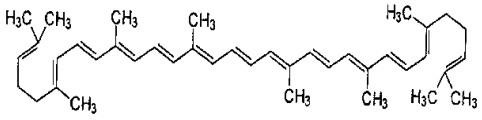
AsX is a dark-red pigment found primarily on marine algae and aquatic animals. It is a ketocarotenoid found in a variety of shellfish and birds, including salmon, trout, red sea bream, shrimp, lobster, flamingos, quails etc. The green algae *Haematococcus pluvialis*, red yeast *Phaffia rhodozyma*, *Chlorella zofingiensis, Chlorococcum sp.*, and the marine bacterium *Agrobacterium aurantiacum*, as well as crustacean by-products, are the familiar sources of natural AsX ( Jyotika, *et al*., 2012). *H. pluvialis*, a microalga, has the highest ability to accumulate AsX, up to 4–5% of dry cell weight (Yuan *et al*., 2011). AsX possess several health-promoting effects in the prevention and treatment of a variety of diseases, such as cancer, chronic inflammatory diseases, metabolic syndrome, diabetes, diabetic nephropathy, cardiovascular diseases, gastrointestinal diseases, liver diseases, neurodegenerative diseases, eye diseases, skin diseases, exercise-induced fatigue, male infertility, and anaemia. Several investigations have shown that AsX possesses antioxidant properties. Regarding free radical antioxidant activity, AsX can outperform vitamin E and β-carotene by up to several times (Shimidzu *et al*., 1996).

AsX, popularly known as "super vitamin E," contains ten times the antioxidant activity of other carotenoids like Zeaxanthin, Lutein, Canthaxanthin, and β-carotene and 100 times the antioxidant activity of α-tocopherol (Higuera-Ciapara *et al*. 2006). Because of its molecular structure, AsX possesses unique chemical characteristics. The more significant antioxidant activity is due to hydroxyl and keto moieties on each ionone ring (Kishimoto *et al*., 2010). Besides the health benefits of AsX, recent research has revealed the role of AsX in the gut microbiota linked to various diseases (Table 2).

It was reported that AsX affects the activities of the intestinal mucosa in Cyclophosphamide-induced immune-deficient mice (Zhang *et al*., 2020). They found a change in the composition of the gut flora and its metabolites after administering AsX. *Lactobacillus* and *Bifidobacteria*, beneficial probiotic bacteria, were significantly reduced in the control group. At the same time, they were higher in the β-carotene control and AsX-treated groups. In contrast, immune-deficient mice had higher levels of commensal bacteria such as *Clostridium coccoides, Enterobacteriaceae spp*., and *Enterococcus spp* (Fig. 4).

On the other hand, *C. coccoide* and *Enterobacteriaceae spp*. were significantly reduced in the β-carotene group and the AM (AsX medium-dose- 60 mg/kg b.w) groups. The AM and AH (AsX high dose- 120 mg/kg b.w) groups had a more similar composition of major intestinal bacteria to the control group than the other groups. Short-chain fatty acids (SCFA) estimation revealed that the control group had the lowest total SCFAs, whereas intervention with β-carotene and AsX increased total SCFAs. Furthermore, propionic acid and butyric acid levels in immune-deficient mice had reduced by 62% and 35%, respectively. They were significantly higher in the β-carotene group and the AH group. These findings suggested that β-carotene or ASX could help to speed up the formation of SCFAs. SCFAs, particularly acetic acid, propionic acid, and butyric acid, are essential bacterial metabolites in modulating intestinal immunity, lowering intestinal inflammation, and improving intestinal

**Table 1.** Natural sources of different types of carotenoids

| Dietary Carotenoid | Structure | Source | References |
|---|---|---|---|
| Astaxanthin |  | *Adonis annua* flowers, fungi, algae, bacteria, shrimp | Saini *et al*., 2022 |
| β-carotene |  | Carrots, fungi, algae, bacteria, fruits and all green vegetables (e.g: apricot, cantaloupe, mango, carrots, red peppers, sweet potatoes, pumpkins, spinach, broccoli, chard and kale) | Saini *et al*., 2022 |
| α-carotene (combination with β-carotene) |  | Green leafy vegetables (e.g. carrots) and some varieties of squash, and pumpkins | Saini *et al*., 2022 |
| Canthaxanthin |  | Crustaceans, fungi (*Cantharellus sp.),* algae | Takaichi *et al*., 2011 |
| Capsanthin |  | Red pepper (*Paprika - Capsicum annuum*) | Takaichi *et al*., 2011 |
| Cryptoxanthin |  | Extensively found in low amounts in many tropical orangefleshed fruits (e.g., oranges, mangos, ripe red and orange peppers, mandarins, papayas, pumpkin, yellow maize, seaweed, peaches, nuts and persimmons) | Saini *et al*., 2022 |
| Lutein |  | Green vegetables (e.g., squash, broccoli, peas, brussels sprouts, string, beans) | Saini *et al*., 2022 |
| Zeaxanthin |  | Egg yolks, certain yellow-orange fruits (e.g. squash, oranges) and dark leafy green vegetables | Takaichi *et al*., 2011 |
| Lycopene |  | Alfalfa, tomato, watermelon, pink grapefruit, papaya, guava, rose hip, fungi | Takaichi *et al*., 2011 |

Source: Saini *et al*., 2022; Takaichi *et al*., 2011

functioning (Zhang *et al*., 2020).

Another study reported that, while modulating the variety of cecal microbiota, AsX reduced Ochratoxin A (OTA)-induced cecum damage and inflammation in mice (Chen *et al*., 2021). They observed that OTA decreased gut flora diversity and increased the number of *Firmicutes* and *Lactobacillaceae.* The number of intestinal pathogens is inversely proportional to the abundance of *Firmicutes* (Mulder *et al*., 2009). Changes in lactobacillus proportions induce the alteration in the abundance of *Firmicutes*, indicating that *lactobacillus* is a primary detoxifying bacteria in the OTA group (Walter,2008). Moreover, OTA decreased the number of *Lachnospiraceae* but recovered with ASX supplementation. AsX treatment improved gut flora and increased gut microbial diversity (especially *Lactobacillaceae* and *Lachnospiraceae*), leading to cecum barrier recovery from OTA-induced injury.

A study investigated the role of AsX on mouse gut mi-

crobiota to inhibit alcoholic fatty liver disease (Liu *et al*., 2018). They reported that ethanol and AsX supplementation considerably impacted specific bacterial populations. *Bacteroidetes*, including the genera *Bacteroides, Butyricimonas*, and *Parabacteroides* were substantially more common in the disease model group (Ethanol-induced Alcoholic Fatty Liver Disease (AFLD) group). *Bacteroides* are the most prevalent genus observed in alcohol-fed mice (Yan *et al*., 2012; Lowe *et al*., 2017; Neyrinck *et al*., 2017)

They also found that AsX intervention significantly reversed the ethanol-induced increase in *Bacteroidetes* and *Proteobacteria*, restoring their proportions to the regular diet group. *Proteobacteria* can grow in the gut as a pro-inflammatory intestinal microorganism in response to an imbalanced microbial composition (Shin *et al*., 2015), suggesting that AsX's anti-inflammatory properties are likely to be responsible for its protective effects. Furthermore, they observed a drop in Akkermansia *(Akk)* abundance in ethanol-exposed AFLD mice, which was reversed by AsX treatment, bringing it back to levels even higher than the control group indicating that AsX supplementation help mice with AFLD by enhancing *Akk.* Lack of *Akk* is an early indicator of gut dysbiosis caused by alcohol (Liu *et al*., 2018).

Further, ethanol exposure diminishes the number of *Akk* in both mice and humans, and oral supplementation alleviated the status of AFLD, suggesting the bacterium's protective action on AFLD. They also reported that the ethanol diet considerably increased the species of *Butyricimonas, Oscillospira, Clostridiales, Bilophila* and AsX supplementation significantly reduced it. *Oscillospira* and *Clostridales* increase during the inflammatory response, linked to intestinal mucosa barrier damage (Power *et al*., 2016; Mastrocola *et al*., 2018). These findings suggest that AsX alleviates the AFLD phenotype by enriching the essential bacteria for gut integrity and anti-inflammation.

Wu *et al*., (2020), investigated the effect of AsX on gut microbiota, inflammation, and whole-body metabolic homeostasis in wild-type C57BL/6 J and, β-carotene 9′, 10′-dioxygenase (BCO2) knockout (KO) mice. The study demonstrated the interplay between gender, diet, and genotype in gut microbiota homeostasis and host metabolism. 16S rRNA sequencing revealed a gender-specific association of gut microbiota, which might present distinct responses to dietary AsX supplementation. *Bacteroidetes* and *Proteobacteria* were significantly higher, whereas the Firmicutes*/Bacteroidetes* (F/B) ratio and *Actinobacteria* abundance were substantially lower in females than males. In addition, they found that female mice had higher fecal SCFA concentrations and abundance of *Lachnospiraceae* bacterium (*Firmicutes*) and lower *Ruminococcus (Firmicutes)* than male mice. *Lanchnospiraceae* species ferment undigested food fibres to create SCFAs (Tanca *et al*. 2018). SCFAs decrease systemic inflammation by promoting commensal bacterial growth and host epithelial regeneration (Xu *et al*., 2018) showed that changes in glucose and lipid metabolism are due to a shift in the gut microbiota. *M. schaedleri* was significantly enhanced in BCO2-deficient animals, regardless of gender, and was highly related to numerous metabolic parameters, including fasting blood glucose, fat percentage, and cholesterol. According to previous investigations, increased *M. schaedleri* abundance in the gut is related to local and systemic inflammatory responses (Daniel *et al*., 2017; Loy *et al*., 2017). Hence, variations in *M. schaedleri* abundance could be a biomarker for BCO2 protein expression status in mice.

sX supplementation in male knock-out mice increased the number of *Akk. muciniphila (Verrucomicrobia)* substantially compared to malewild-type mice. *Akk. muciniphila* is amucin-degrading bacterium that safeguards the intestinal mucus layer. Indeed, serum carotenoid levels signify the proliferation of *A. muciniphila* in the intestine. *A. muciniphila* enrichment protects mouse white adipose tissues from inflammation caused by high saturated lipid levels following high-fat diet-induced (Caesar *et al*., 2015; Djuric *et al*., 2018; He *et al*., 2018), whereas quantity of *Proteobacteria* is lowered in KO mice. Increased *Proteobacteria* populations are linked to inflammation and are considered as a hallmark of microbiome imbalance and a contributing factor to cecal inflammation (Carvalho *et al*., 2012). Thus, AsX promotes gut microbiota homeostasis by increasing the abundance of beneficial bacteria (such as *A. muciniphila*) while decreasing harmful bacterial growth

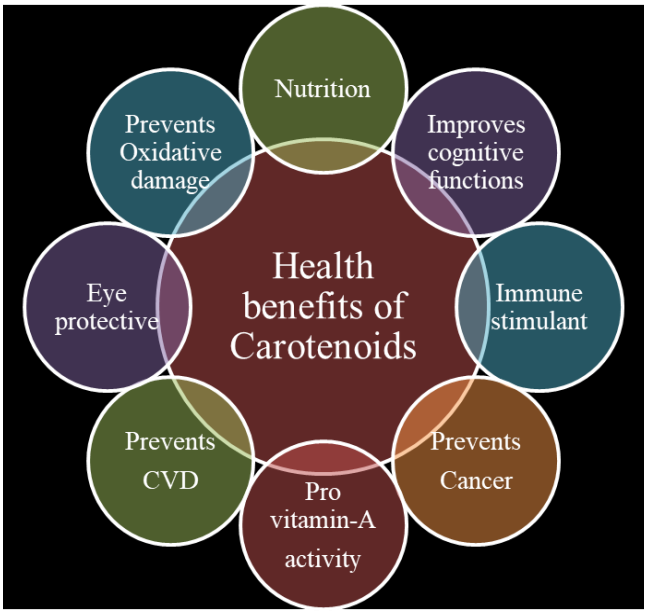



**Fig. 3.** *Role of carotenoids in human health and disease (Source: Olatunde et al., 2020)*

**Table 2.** Effect of Astaxanthin on the gut microbiome in different disease models

| Dietary Carotenoid | Disease model | Gut microbes altered | References |
|---|---|---|---|
| **Astaxanthin** | Cyclophosphamide - induced immunodeficient mice | *Lactobacillus* ↑<br>*Bifidobacteria* ↑<br>*Clostridium coccoides* ↓<br>*Enterobacteriaceae spp*. ↓<br>*Enterococcus spp.* ↓ | (Zhang *et al*., 2020) |
| | OTA-induced cecum damage and inflammation in mice | *Firmicutes* ↓<br>*Lactobacillaceae* ↑<br>*Lachnospiraceae* ↑<br>*Bacteroides* ↓<br>*Butyricimonas* ↓ *Parabacteroides* ↑ | (Chen *et al*., 2021) |
| | AFLD in mice | *Proteobacteria* ↓<br>*Akk* ↑<br>*Butyricimonas* ↓<br>*Oscillospira* ↓<br>*Clostridiales* ↓<br>*Bilophila* ↓ | (Liu *et al*., 2018) |
| | Wild-type C57BL/6 J and BCO2 KO mice | *Akk. muciniphila* ↑<br>*Proteobacteria* ↓ | (Wu *et al*., 2020) |
| | High fat diet (HFD) induced obese mice | *Firmicutes/Bacteroides* ↓<br>*Proteobacteria* ↓<br>*Akk* ↑ | ( Backhed *et al*., 2004) |

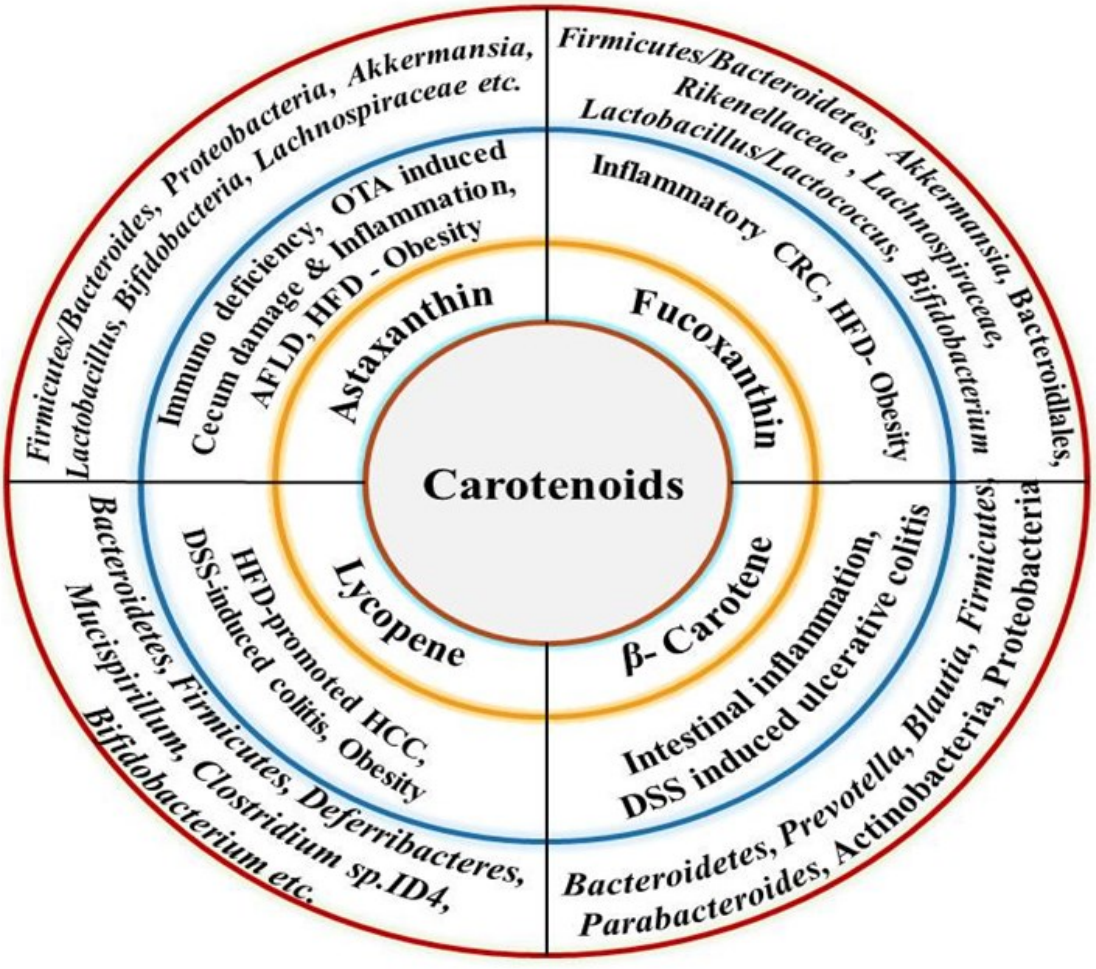



**Fig. 4.** *Action of major dietary carotenoids on gut microbiome in different disease models*

(such as *Proteobacteria*). Hence AsX significantly impacts the gut microbiota by reducing local and systemic oxidative stress and inflammation.

Wang *et al*. (2019) found that *Xanthophyllomyces dendrorhous* derived AsX had a regulatory influence on lipid metabolism and gut microbiota in high-fat diet-induced obese mice, and adding AsX or X*. dendrorhous* powder to a high-fat meal lowered the *Firmicutes/Bacteroides* ratio. The *Firmicutes* to *Bacteroidetes* ratio is crucial for bodyweight variations (Backhed *et al*., 2004)preventing *Proteobacteria* growth, which is beneficial for health. Increased *Proteobacteria* prevalence is a possible diagnostic signature of dysbiosis and illness risk (Shin *et al*., 2015). *Proteobacteria* flourished in the gut due to a high-fat diet, causing illnesses. Addition of AsX or *X. dendrorhous* powder to the gut enhanced the amount of *Akk*. *Akk* draws energy from the mucin produced by the mucosa, thereby guarding the gut against infections through competition (Belzer and De Vos, 2012) by adhering to the gut mucosa. Previous research has shown that feeding mice live *Akk* can prevent diet-induced obesity while having little effect on their appetite or eating behaviour (Everard *et al*., 2013). A high-fat diet and a large amount of alcohol intake will lower the amount of *Akk* in the gut. In conclusion, AsX and *X. dendrorhous* powder had a beneficial regulatory effect on gut microbiota, ensuring the health of gut micro-ecology and preventing obesity due to a high-fat diet.

**Effect of fucoxanthin on gut microbiota**

Fx is an important carotenoid contributing around 10% of the overall production of carotenoids in nature. It has a unique structure containing an uncommon allenic bond, a 5, 6-monoepoxide (Kim and Pangestuti, 2011), and a polyene chain conjugated to a carbonyl group. This unique structural characteristic cause Fx's antioxidant, anti-inflammatory, and anticancer properties. Fx is an exceedingly polar carotenoid commonly present algae, consisting of *Undaria pinnatifida, Laminaria japonica, Phaeodactylum tricornutum,* and *Cylindrotheca closterium* (Zhang *et al*., 2015). Intestinal microbes hydrolyze Fx into fucoxanthinol, hence enhancing its bioavailability ( Liu *et al*., 2019).

Guo *et al*., 2019 investigated the impact of Fx on microbial profiles of caecal and faecal samples from BALB/c mice fed with HFD, confirmed the changes in *Firmicutes/Bacteroidetes* ratio and the abundance of S24-7 and *Akk* indicated the anti-obesity activity of Fx. Another group led by Liu *et al*. (2019), reported the impact of Fx isolated from edible algae *Undaria pinnatifida* on pathogenic microorganism *Escherichia coli* and *Lactobacillus* in invitro and invivo models wherein, Fx strongly inhibited the growth of Gram-positive pathogenic microorganisms but was less effective towards Gram-negative microorganisms and promoted the growth of intestinal microbes in mice (Table 3).

Terasaki *et al*., (2018), investigated the chemoprotective effect of Fx and its impact on gut microbiota in a mouse model of inflammatory colorectal cancers showed the inhibition of multiplicity of colorectal adenocarcinoma upon administration of Fx (30 mg/kg BW) for 14-week. Fx administration notably suppressed *Bacteroidales* and *Rikenellaceae* and increased *Lachnospiraceae* population compared with the control mice. Oral administration of a faecal suspension acquired from Fx-treated mice aimed to increase *Lachnospiraceae*, suppress the number of colorectal adenocarcinomas in Azoxymethane and Dextran sodium sulphate (AOM/DSS) treated mice with an increase in *Lachnospiraceae* in the gut. Their findings suggested that an alteration in gut microbiota by Fx is probably an essential factor in the chemoprotective impact of Fx in AOM/DSS- treated mice (Fig. 4).

Sun *et al*. (2020), designed a mouse model to study the modulation of gut microbiota by Fx to Richards intestinal microbial homeostasis. Fx also reduced HFD-induced gut microbiota dysbiosis by suppressing the growth of obesity/inflammation-related *Lachnospiraceae* and *Erysipelotrichaceae* while boosting the growth of *Lactobacillus* / *Lactococcus*, *Bifidobacterium*, and some butyrate-producing bacteria as confirmed by its 16S rRNA sequencing.

**Effect of lycopene on gut microbiota**

LYC is a lipophilic, unsaturated, biologically active acyclic carotenoid found in fruits and vegetables that are red in colours, such as tomato, papaya, pink grapefruit, pink guava, and watermelon. Processed tomato products like ketchup, tomato juice, spaghetti sauce, and pizza sauce account for more than 80% of dietary LYC consumption, as processing generally entails water loss. Hence, the amount of LYC processed foods is often significantly higher than that in fresh foods (Xia *et al*., 2018). According to Zhao B *et al*., 2018, LYC-containing foods, such as tomato products and supplements, affect a wide range of illnesses, including cancer, heart disease, and asthma. LYC exhibits anti-atherosclerotic, antioxidant, anti-inflammatory, anti-hypertensive, anti-platelet, anti-apoptotic, and protective endothelial effects (Table 4). LYC showed the prevention of malignancies such as Osteosarcoma, lung, and prostate cancers due to its antioxidant properties. Unlike most carotenoids, LYC does not convert to Vitamin A in human bodies (Story *et al*., 2010; Mozos *et al*., 2018).

LYC-containing dietary tomato powder (TP) feeding showed the suppression of HFD-promoted hepatocellular carcinoma (HCC) development andprotected HFD-induced inflammation with putative gut microbiota mod-

ulation (Editorial 2007). A 16s rDNA sequencing study showed that TP feeding boosted the richness of the gut microbiome and a significant increase in microbial diversity in the HFD + DEN (Diethyl Nitrosamine, a liver-specific carcinogen) group in a BCO1/BCO2 double KO mice (Xia *et al*., 2018). The relative abundance of gram -positive bacteria increased following TP feeding, whereas gram-negative bacteria decreased. According to phylum-level analysis, six main phyla (*Bacteroidetes,* Firmicutes*, Deferribacteres, Proteobacteria,Actinobacteria,* and *Tenericutes)* dominate the fecal microbiota (Fig 4).

Although Gram-positive and gram-negative bacteria coexist in the gut, Gram-negative bacteria overgrowth can increase the generation of hepatotoxic chemicals like lipopolysaccharide (LPS) (Wigg *et al*., 2001). They observed the species of Deferribacteres and a relative abundance of *Mucispirillum* and *Mucispirillum Schaedler* reduced drastically following TP feeding. *Mucispirillum* cause increased serum leptin levels and inflammatory markers (Loy *et al*., 2017), suggested that TP feeding could reduce inflammatory cytokines by reducing Mucispirillum's gut microbiota. The Clostridium sp.ID4 and Clostridium sp.Clone.9 populations in the TP feeding group also showed a decline and an increase in the TP feeding group, respectively. Hepatic lipogenesis and fat oxidation have increased by *Clostridium* species (Nadeau and Conjeevaram, 2017). Together, Gut-liver interaction and TP feeding boosted the gut microbiome's richness and diversity and improved some beneficial bacteria.

Zhao *et al*. (2020), found a correlation between LYC consumption and gut microbiota structure and metabolite production in DSS-induced colitis mice. They reported that *Firmicutes, Actinobacteria*, and *TM7* had increased relative abundance in both the control and LYC treatment groups compared to DSS group, but *Proteobacteria* and *Deferribacteres* had higher relative abundance in the DSS group. The relative abundance of *Clostridiales* and *Lachnospiraceae* in the SCFAs of gut microbiota in the DSS group was much lower than in the control group. DSS increased the relative abundance of *Mucispirillum,* whereas the relative abundance of probiotic bacteria (*Lactobacillus* and *Bifido- bacterium)* was decreased. SCFAs like acetate, propionate, isobutyrate, butyrate, valerate and isovalerate are significantly reduced but, LYC increased the concentrations in DSS-induced colitis mice. LYC could influence the relative abundance of gut microbiota and its metabolic products. As a result, LYC affected DSS-induced changes in gut microbiota metabolites, including LPS and SCFAs. The gut microbiota structure of DSS-induced colitis mice was altered by LYC, suggesting that the gut-brain axis balance may also play a role.

Wiese *et al*. (2019) explored the systemic effect of LYC and dark chocolate (DC) on gut microbiota, blood, liver metabolism, skeletal muscle tissue oxygenation and skin in moderately obese individuals. After four weeks of supplementation with GA-LYC (GAL) (GAL - is added to overcome reduced bioavailability in older people and individuals with metabolic syndrome), followed by 16s rRNA sequencing of gut microbiota from faeces demonstrated a shift in gut microbial communities. They found GAL formulations resulted in a dose-dependent increase in members of the phyla Actinobacteria, primarily due to the rise in the relative abundance of *Bifidobacterium spp*. and *Lactobacilli* spp. implied the prebiotic potential. They also observed that continuous intervention with GAL, DC, and DCL (DC+LYC) resulted in a considerable reduction in *Bacteroidetes* abundancedue to the direct impact or its indirect activity via stimulation of *Bifidobacteria* species or a combination of both.

**Effect of β-carotene on gut microbiota**

In certain fruits and vegetables, β-carotene is a retinol precursor (Vitamin A). It is a cyclic carotene with yellow colour. The most active and significant provitamin-A carotenoid has a bright red-orange colour and is commonly found in plants and fruits. It has multiple roles in the biological system as a natural pigment, provitamin-A, plant metabolite, human metabolite, mouse metabo-

**Table 3.** Effect of fucoxanthin on gut microbiome in different disease models

| Dietary Carotenoid | Disease model | Gut microbes altered | References |
|---|---|---|---|
| **Fucoxanthin** | HFD fed BALB/c mice | *Firmicutes/Bacteroidetes*↓<br>S24-7 ↑<br>*Akk*↓ | (Guo *et al*.,2019) |
| | Inflammatory colorectal cancers in mouse | Bacteroidlales↓<br>*Rikenellaceae* ↓<br>*Lachnospiraceae* ↑ | (Terasaki *et al*.,2020) |
| | HFD induced obese mice | *Lachnospiraceae*↓<br>*Erysipelotrichaceae*↓<br>*Lactobacillus/Lactococcus* ↑<br>*Bifidobacterium* ↑ | (Sun *et al*., 2020) |

lite, cofactor, andantioxidant (beta-Carotene | C40H56 - PubChem https://pubchem.ncbi.nlm.nih.gov/compound/beta-Carotene).

β-Carotene is one of the most widely studied carotenoids for its vitamin-A activity, abundant in fruits and vegetables. Apricots, Asparagus, Broccoli, Carrots, Chinese cabbage, Onions, Peas, Peppers, Plums, Pumpkin, Spinach, Squash, and Sweet Potatoes are rich in β-Carotene. β-carotene can also be extracted from halo-tolerant algae *(Dunaliella salina)* or fungi *(Blakeslea trispora)*. Epidemiological studies have proved the abundance of dietary carotenoids as being protective against many diseases (Table5). β-carotene protects membrane lipids from free radical damage by scavenging singlet oxygen, cleaning peroxide radicals, and interacting directly with peroxy radicals. β-carotene improves cognitive function in addition to its antioxidant activity. Long-term intake of β-carotene for 15 years or more may slow down age-related cognitive decline, but short-term intake has no significant effect (Grodstein *et al*., 2007; Kristine, 2007). It also helps to improve skin health, which is likely due to its antioxidant effects (Stahl and Sies, 2012). Diets high in carotenoids, such as β-carotene, may aid in eye health and protect against illnesses of the eyes, such as age-related macular degeneration (AMD). High blood levels of carotenoids, such as β -carotene, have been demonstrated in studies to lessen the chance of developing advanced age-related macular degeneration (Wu *et al*., 2016). Furthermore, diets rich in beta carotene-containing fruits and vegetables may be particularly efficient in lowering the incidence of AMD in smokers (Kim *et al*., 2017) and preventing lung cancer (Cai *et al*., 2019); further, evidence of β-carotene's effect on gut microbial dysbiosis exists.

Li *et al*., (2019) demonstrated that β-carotene reduces weaning-induced intestinal inflammation in piglets by modifying gut flora. Their findings showed that β-carotene improved growth performance, intestinal morphology, and relieving inflammation. Furthermore, compared to the weaning group, β-carotene considerably decreased species of the phyla *Bacteroidetes* and the genera *Prevotella* and *Blautia*, and significantly increased species of the phyla *Firmicutes,* genera p-75-a5, *Parabacteroides*. *Prevotella* and *Blautia* were positively correlated, whereas, *Parabacteroides* and Synergists were negatively correlated with the levels of IL-1β, IL-6, and TNF-α. At the same time, p-75-a5 showed a negative correlation with IL-6 in piglet serum samples. These data suggest that β-carotene reduces weaning-induced intestinal inflammation in pigs via altering the gut microbiome. *Prevotella* could target β-carotene in piglets suffering from weaning-induced intestinal inflammation (Fig. 4).

Zhu *et al*., (2021) investigated the effects of β-carotene on gut microbiota modulation and its anti-inflammatory effects in a rat model of ulcerative colitis induced by dextran sulphate sodium (DSS). Their 16S rRNA sequencing approach demonstrated that the relative abundance of gut microbiota changed dramatically with DSS administration at the phylum and genus levels. Furthermore, β-carotene treatment enhanced the population of certain beneficial microorganisms and is negatively correlated with inflammatory cytokine levels.

Firmicutes and Actinobacteria had low relative abundance in DSS group, while Bacteroidetes and Proteobacteria were higher. On the other hand, treatment with β-carotene boosted the abundance of Firmicutes and Actinobacteria while decreasing the abundance of Bacteroidetes and Proteobacteria. The Bacteroidetes phylum in humans and animals contains three essential bacteria that can turn dangerous; hence their micro-ecological imbalance may lead to endogenous infection (Gilmore, 2008; Liu *et al*., 2018). The increase in *Proteobacteria* is a warning sign of disease (Yan *et al*., 2012).

The correlations between gut bacteria and serum inflammatory cytokine levels revealed that only *Faecalibacterium* was inversely correlated with inflammatory cytokine levels, whereas the others were favourably correlated. *Faecalibacterium* is one of the most common butyrate-producing bacteria among gut microbes and has a negative correlation with disease activity in inflammatory bowel disease patients (Lopez-Siles *et al*., 2017; Pittayanon *et al*., 2020). *Faecalibacterium* has anti-inflammatory capabilities and can promote epithelial cell proliferation and repair to sustain the intestinal mucosal barrier's integrity and gut health (Sokol *et al*., 2017). *Staphylococcus, Sutterella,* and *Parabacteroides* were highly expressed in the DSS group and positively associated with TNF-α. Most *Staphylococcus* species are conditional pathogens that cause infection and are common in IBD patients. *Sutterella* is commonly observed in patients with gastrointestinal problems linked to inflammation in the intestine. DSS-induced chronic colitis dramatically enhances the abundance of *Sutterella* in mice (Cai *et al*., 2019; T. Liu *et al*., 2019). *Alistipes* and *Phascolarctobacterium* were more prevalent in the DSS group, and both had significantly correlated with IL-6 and IL-1 levels. *Alistipes* have been associated with colon rectum cancer, while *Phascolarcto bacterium* is associated with diarrhoea (Seishima *et al*., 2019). *Veillonella* and *Enterococcus* were also more prevalent in the DSS group and were strongly related to IFN-γ. Both *Veillonella* and *Enterococcus* are pathogens, and studies have shown that *Veillonella* raises the risk of colitis, while *Enterococcus* can cause colon illness and an imbalance in inflammation factors (Abdel-Aal *et al*., 2013; Santoru *et al*., 2017). These findings suggest that β-carotene's anti-inflammatory actions are

**Table 4.** Effect of Lycopene on the Gut microbiome in different disease models

| Dietary Carotenoid | Disease model | Gut microbes altered | References |
|---|---|---|---|
| **Lycopene** | HFD-promoted Hepato cellular carcinoma in mice | *Bacteroidetes*↑<br>*Firmicutes*↑<br>*Deferribacteres*↑<br>*Proteobacteria*↑<br>*Actiobacteria*↑<br>*Tenericutes*↑<br>*Deferribacteres*↓<br>Mucispirillum ↓<br>Mucispirillum schaedleri↓<br>*Clostridium sp*.ID4 ↓<br>*Clostridium sp*.Clone.9 ↓ | (Xia *et al*.,2018) |
| | DSS-induced colitis in mice | Firmicutes↑<br>Actinobacteria↑<br>TM7↑<br>*Proteobacteria*↓<br>*Deferribacteres*↓ | (Nadeau and Conjeevaram, 2017) |
| | Moderately obese individuals | *Bifidobacterium longum*↑<br>*Bifidobacterium adolescentis*↑<br>*Lactobacilli* spp↑<br>Bacteroidetes↓ | (Wiese *et al*., 2019) |

**Table 5.** Effect of β-carotene on the gut microbiome in different disease models

| Dietary Carotenoid | Disease model | Gut microbes altered | References |
|---|---|---|---|
| **β-carotene** | Weaning-induced intestinal inflammation in piglets | *Bacteroidetes*↓<br>*Prevotella*↓<br>*Blautia*↓<br>*Firmicutes*↑<br>p-75-a5↑<br>*Parabacteroides*↑ | (Li *et al*.,2019) |
| | DSS induced ulcerative colitis in rats | Firmicutes↑<br>Actinobacteria↑<br>Bacteroidetes↓<br>Proteobacteria↓ | (Zhu *et al*., 2021) |

mediated by altering the gut flora through the inflammatory factor.

Apart from these carotenoids, some unique carotenoids also substantially affected gut microbiota, such as Leutin and Crocetin. Lutein naturally occurs in several fruits and vegetables, orange, and reddish-yellow colored vegetables like kale, spinach, broccoli, parsley, leek, red pepper, peas, lettuce, and also in egg yolks (Lin *et al*., 2021). Lutein supplements were used in alternative medicine for eye diseases, such as cataracts and macular degeneration. Alternative medicine proponents claim that lutein supplements can also help prevent colon cancer, breast cancer, diabetes, and heart disease. To date, most of the studies on lutein's health benefits have focused on its dietary intake, suggesting that lutein may help protect against atherosclerosis, age-related macular degeneration, and cataracts.

Therefore, it is evident that there is a differential expression of gut bacteria upon administration of different carotenoids. The differential expression includes alterations in the abundance of certain microbial taxa or structure of the microbial community, decreased bacterial richness and/or diversity and decreased microbial community stability.

## Conclusion

The current active field of research in biomedicine is on the human gut microbiome; its dysbiosis in various disease models indicates the importance of the involvement of the gut microbiome in human health and disease. Various studies have revealed the major differences in microbial taxonomic and functional composition in different disease conditions compared to their normal counterparts. It is still under debate, whether dysbiosis precedes the development of disease and

sets the inflammatory process or merely reflects the inflamed mucosa's altered immune and metabolic environment. Therefore, it is essential to study newly diagnosed treatment-naïve patients, where the microbiome can be studied at the beginning of the disease.

**Future perspectives**

Currently, Gut microbiome studies are mainly focused on bacteria, and the gut microbiome is composed of other microorganisms beyond bacteria, such as viruses, fungi or archaea, which play a role in human health and disease other than the bacterial population *per se*. Therefore, future studies should include a holistic approach with respect to the gut microbiome for a deeper understanding of the specific disease. The available microbiome data represent a valuable data source that can be utilized for identifying associations between the microbiome and specific disease conditions upon administration of specified carotenoids along with their pathophysiological understanding may help in promoting the development of clinical strategies, including disease prevention, treatment, stratification and assessment of the high-risk population. As there is a great diversity in the composition of microbial taxa diversity between individuals and within the same individual over time, the predictive value of these potential indicators has low clinical importance. In order to use the gut microbiome as non-invasive biomarkers in human disease, prospective longitudinal studies on gut dysbiosis in early-onset of specific disease conditions are warranted to enable personalized treatments and to reduce the health care economic burden.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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