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Impact of carotenoids on ulcerative colitis induced colorectal cancer – A review

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Abstract

Ulcerative colitis (UC) is one of the major forms of irritable bowel disease that is characterized by chronic inflammation of the colon and may progress into colorectal cancer (CRC), which is the second most deadly cancer all in the world. Some inflammatory mediators like tumor necrosis factor alpha (TNFα) increases resulting in a repeated cycle of inflammation leading to UC. Chronic inflammation found in CRC is believed to be due to induction of cytokines (as T cells and macrophage) and chemokines leading to alterations in proliferation, survival, and migration of epithelial cells. Particularly, inflammatory signaling pathways such as nuclear factor kappa B (NF-κB), interleukin-6 (IL-6)/ Signal transducer and activator of transcription 3 (STAT3), cyclooxygenase-2 (COX-2) / prostaglandin (PGE2), and IL-23/ T-helper (Th17) have been identified in the propagation of UC related CRC and non-colitis related CRC. UC induced CRC is treated with anti-inflammatory drugs but may be associated with side effects. Therefore, this review is to highlight the pathogenesis of UC induced CRC and to explore the potential role of natural drugs such as carotenoids in the treatment of UC and CRC.

Key words: Carotenoids; Natural anti-inflammatory; Ulcerative colitis; Colo rectal cancer.

List of abbreviations

APC: Adenomatous polyposis coli; Bcl-2: Beta cell lymphoma-2; Cat: Catalase; CXCL8: Chemokine (C-X-C motif) ligand 8; CIN: Chromosomal instability; CRC: Colorectal cancer; COX-2: Cyclooxygenase-2; DSS: Dextran sulfate

sodium; EGFR: Epidermal growth factor receptor; GSH: Glutathione; iNOS: Inducible nitric oxide synthase; IBD: Inflammatory bowel disease; IGF: Insulin growth factor; IFNγ: Interferon gamma; IL: Interleukin; JNK: Jun N-terminal kinase; KRAS: Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; lncRNA: Long non-coding RNA; MDA: Malondialdehyde; MMP: Matrix metalloproteinase; miRNA: Micro RNA; MSI: Microsatellite instability; MAdCAM-1: Mucosal vascular addressing-cell adhesion molecule-1; NO: Nitric oxide; NF-κB: Nuclear factor kappa B; PSC: Primary sclerosis cholangitis; PGE: Prostaglandins; RAS: Rat sarcoma virus; STAT3: Signal transducer and activator of transcription 3; Th: T helper; TGF: Transforming growth factor; TNFα: Tumor necrosis factor alpha; UC: Ulcerative colitis.

1. Introduction

Inflammatory bowel disease (IBD) is an emerging and global disease. Ulcerative colitis (UC) and Crohn's disease are the major forms of IBD [1]. Due to its chronic condition, the hospitalization rate of IBD increased tragically, especially for UC [2].

Moreover, UC is an idiopathic, chronic inflammatory condition of the colonic mucosa that begins in the rectum and progresses proximally over a portion of the entire colon [3]. The incidence of UC has increased in many newly industrialized countries in South America, Asia, Africa, and the Middle East [1]. UC has an incidence of 9 to 20 cases per 100,000 persons per year. Its prevalence is 156 to 291 cases per 100,000 persons per year [4]. Therefore, this review aims to investigate the pathogenesis of UC induced CRC and to explore the potential role of natural drugs such as carotenoids in the treatment of UC and CRC.

2. Ulcerative Colitis

2.1. Risk factors of ulcerative colitis

2.1.1. Modifiable Risk Factors

2.1.1.1. Smoking

Smoking is the major risk factor for UC by inhibiting the gut mucosa and increasing the inflammatory response thus aggravating UC. It may form DNA adducts resulting in the aggressive conversion of UC to colon cancer [5, 6].

On the other hand, smoking may protect against UC. As well, smoking cessation exasperates the disease activity. Moreover, nicotine therapy may be used in some refractory UC cases [7, 8].

2.1.1.2. Diet

There is a relationship between long-term adult dietary macro- and micronutrients and incident IBD. Its role comes from the growing awareness of the importance of gut microbial dysbiosis in the pathogenesis of IBD as well as the impact of both long-term adult diet and short-term alterations on gut microbial diversity and composition, which are important to the pathogenesis of IBD [9].

2.1.1.3. Sleep

Sleeping fewer than 6 hours or more than 9 hours per day is associated with an elevated risk of UC. At 6 months, poor sleep quality during remission is linked to an increased chance of illness relapse [10].

2.1.1.4. Appendectomy

Early appendectomy has been linked to a lower risk of developing UC. The mechanism includes changes in the cluster of differentiation CD4/CD8 ratio and alterations in activated T-cell populations following appendectomy to favor regulatory T cells. The use of therapeutic appendectomy to reduce disease severity and colectomy in patients with UC is not fully clear [9].

2.1.2. Non-modifiable Risk Factor

Ulcerative Colitis is more common in Caucasian people with a mean age of 46 to 62 and it is more common in females than males [11].

2.2. Pathogenesis of ulcerative colitis

Going in-depth, a large sterile mucous layer covers the intestinal barrier under normal physiological conditions. The mucous layer and tight junction act as a barrier to prevent the entrance of pathogens into the laminal environment and circulatory system [12]. Therefore, UC is thought to be caused by the change in mucous layer thickness or impaired mucinous layer resulting in the increase of permeability and defect in the regulation of tight junction **figure (1)**.

The increase in permeability and loose junction result in the microflora entering lamina propria and presented by dendrites cell, which is an antigen representing a cell, produce strong inflammatory mediator as tumor necrosis factor alpha (TNFα) and activates a CD4 and T-cell (CD4 + T-cell). Then, they increase the production of TNFα and Interleukin (IL-12 and IL-4). In addition, TNFα increases the permeability of the mucinous layer. IL-12 leads to activate T-helper (Th1) and produces a proinflammatory mediator; interferon gamma (lFNγ). IL-4 activates Th2 and produces proinflammatory IL-13. These pro-inflammatory mediators are responsible for the inflammation of the colon and rectum **(figure 1, A)** [13].

Moreover, macrophages and dendrites present antigens which produce TNFα leading to up-regulation of mucosal vascular addressing-cell adhesion molecule-1 (MAdCAM-1) on the vascular endothelium of mucosal blood vessels leading to binding of MAdCAM-1 with the specific binding α4β7 that mediates leukocyte return to gut result in inflammation **(figure 1, A, B)** [14].

Furthermore, the production of TNFα from macrophages has a positive feedback mechanism on it making a repeating cycle (**figure 1, B**) [15].

In addition, natural killer T cell is activated by antigen-producing inflammatory mediators IL-13, IL-4 IL-5, and TNFα which are responsible for inflammation **(figure 1, C)** [15].

The inflammation of the colon leads to an increase in chemokine (C-X-C motif) ligand 8 (CXCL8) resulting in the recruitment of leucocytes (**figure 1, D**) [13].

To sum up, TNFα increases the permeability of the mucinous layer that increases antigen which activates macrophage and dendrites cells to produce TNFα resulting in a repeated cycle of inflammation leading to UC.

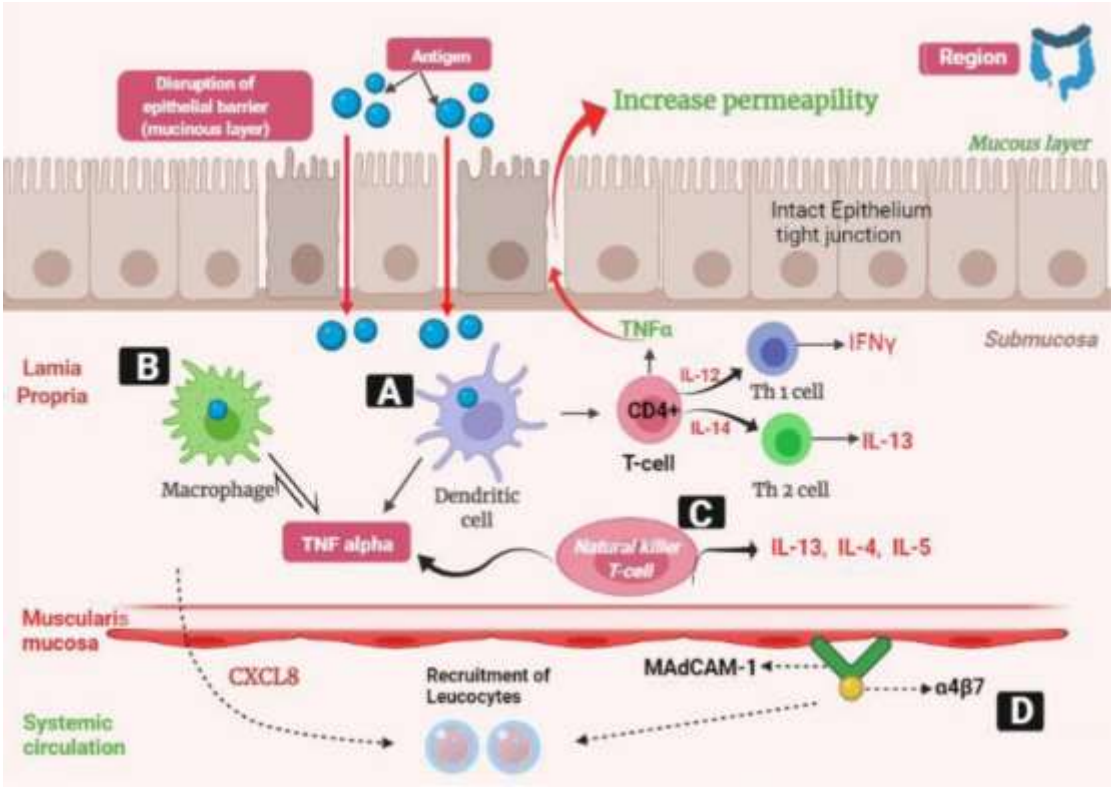

Figure 1: Pathogenesis of ulcerative colitis. (A): Action of dendrites to produce proinflammatory mediator. **(B):** Mechanism of macrophage on production of proinflammatory mediator. **(C):** Natural killer produce proinflammatory mediators. **(D):** Effect of Upregulation of MAdCAM-1 on recruitment of leucocyte. α4β7: Specific binding; CD4: cluster of differentiation; CXCL8: chemokine (C-X-C motif) ligand 8; IL: Interleukin; IFN: Interferon; MAdCAM-1: mucosal vascular addressing-cell adhesion molecule-1; Th: T Helper cell; TNFα: Tumor Necrosis Factor alpha.

On the genetic and epigenetic level, several studies demonstrated UC's pathogenesis. The microRNAs (miRNAs); which are 22 noncoding nucleotides; are found to be associated with inflammation and production of macrophage inflammatory peptides in UC [16, 17].

miRNA-223 is a proinflammatory miRNA that is targeted by inflammatory IL23. miRNA-223 directly inhibits claudin 8 that is the major constituent of the tight junction, and its inhibition disrupts the intestinal barrier resulting in UC [17].

On the other hand, miRNA-148a has an important role in inhibiting UC by decreasing NF-κB and impairing the response of presenting antigen by dendritic cells [18, 19].

Moreover, long non-coding RNA (lncRNA) may inactivate miRNAs or sponge them. LncRNA MEG3 sponges miRNA-98-5p and promotes IL-10; an anti-inflammatory IL; that alleviates UC [20].

2.3. Complications of ulcerative colitis

Figure 2 shows different complications of UC as osteoporosis, colorectal cancer (CRC), perforated colon, toxic megacolon, and sclerosis cholangitis.

2.3.1. Perforated colon

Perforated colon means rupture of colon. It is a life-threatening complication. It happens secondary to weakening of colon due to UC. It may have related to toxic megacolon [21].

It is common in UC patients and who are taking aspirin, nonsteroidal anti-inflammatory drug or steroid [22]. It also occurs mostly in elderly patient and colonic injury associated with endoscopy because of ulceration and chronic inflammation of colon, weakening of colon to certain extent that may form hole in the colon. It is life threatened because colon contains large number of bacteria that may go to abdomen and cause serious infection called peritonitis [21, 23].

2.3.2. Osteoporosis

People with UC generally have high levels of cytokines that boost the body's inflammatory response and involved in deterioration of bones. However, individuals with active forms of Crohn's disease appear to have a higher chance of developing osteoporosis than UC due to higher activity of cytokines. In addition to the poor absorption of vitamin D and calcium in UC that are vital for bone health [24]. Further, the decrease in the release of estrogen; because of prolonged use of corticosteroids utilized in the treatment of UC; accelerates osteoporosis [25].

2.3.3. Primary sclerosis cholangitis

Primary sclerosis cholangitis (PSC) is a rare chronic liver condition in which the bile ducts inside and outside the liver shrink on account of scarring and inflammation. It is commonly linked to UC [26]. About 3–8% of UC patients have PSC. And it was reported from Japan that the frequency of PSC in UC was only 34% [27].

2.3.4. Anti-angiogenesis therapy

Anti-angiogenesis therapy is focused on stopping angiogenesis, which is the process of making new blood vessels; to provide nutrients. Therefore, the goal of anti-angiogenesis therapies is to “starve” the tumor [28].

2.3.5. Toxic megacolon

Toxic megacolon is rare, but potentially deadly complication of UC. It is a nonobstructive acute colonic dilatation (greater than 6 cm in diameter), which can be segmental [29, 30].

The prevalence of toxic megacolon increased with age. About 10% of UC patients complicate into toxic megacolon. It is prevalent in females and of white race followed by blacks [30].

The pathogenesis of toxic megacolon resulting from mucosal inflammation that releases inflammatory mediators, bacterial products and increases the production of inducible nitric oxide synthase (iNOS) which in

turn increases the nitric oxide (NO), and thus causes dilation of the colon [31]. Additionally, toxic megacolon causes inflammation of the smooth muscle of the colon, which leads to paralysis and eventually dilation of the colon [32].

2.3.6. Colorectal cancer

Patients with UC have at least 2-fold increase in the risk of developing CRC [33, 34]. CRC is the third malignant neoplasm and the second most lethal form of cancer. It was estimated to have 1.9 million incidence cases and 900,000 deaths worldwide in 2020 [35-37].

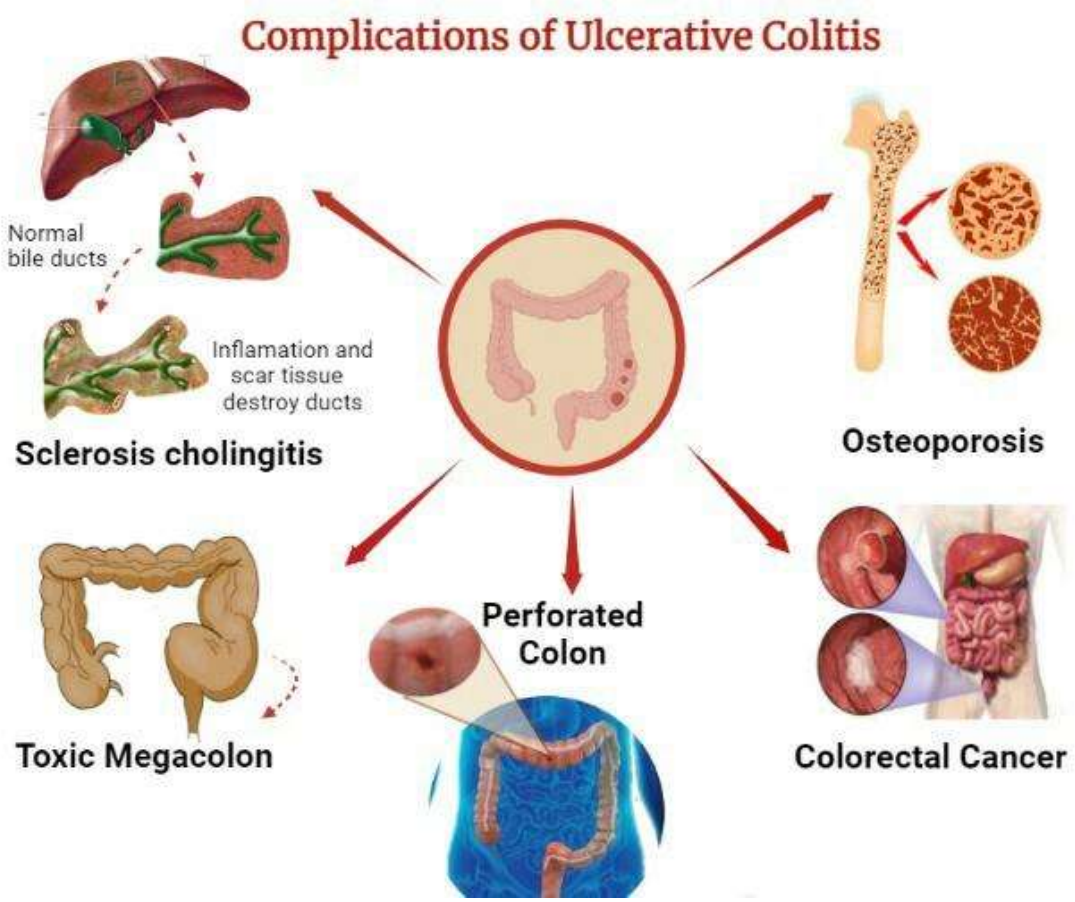

Figure 2: Complications of Ulcerative Colitis.

3. Ulcerative colitis induced CRC

3.1. Pathogenesis of UC induced CRC

Commonly, UC induced CRC occurs due to the release of inflammatory mediators that disrupts intestinal barrier or genetic defects as chromosomal and microsatellite instability (MSI) [38, 39].

Chronic inflammation found in CRC is believed to be due to induction of cytokines (as T cells and macrophage) and chemokines leading to alterations in proliferation, survival, and migration of epithelial cells. Particularly, inflammatory signaling pathways such as nuclear factor kappa B (NF-κB), interleukin-6 (IL-6)/ Signal transducer and activator of transcription 3 (STAT3), cyclooxygenase-2 (COX-2) / prostaglandin (PGE2), and IL-23/ Th17 have been identified in the propagation of UC related CRC and non-colitis related CRC [38, 40, 41].

On the other hand, sporadic CRC is believed to be originated from 1 or 2 foci of dysplasia (abnormal cells in a tissue or organ). UC associated with CRC is thought to be developed from multifocal dysplasia [40]

Chromosomal instability (CIN) and MSI are two of the most common somatic genetic abnormalities that lead to CRC. These two types take place with the same frequency as sporadic CRC but at different times. For example, p53 nutation occurs earlier in UC-associated dysplasia than sporadic CRC while mutations in adenomatous polyposis coli (APC) and Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) genes are known to appear earlier in sporadic CRC than in UC -associated dysplasia [40, 42, 43].

3.2. Treatment of UC-induced CRC

Mesalamines are the first line of therapy for mild to moderate UC induction and remission [44]. Second-line treatment in case of mild to moderate UC who don't response to mesalamine is corticosteroids [45]. Surgery is most common in refractory cases but without complication [44]. For rectal cancer, radiation therapy may be used before surgery, called neo-adjuvant therapy, to shrink the tumor so that it is easier to remove. It may also be used after surgery to destroy any remaining cancer cells. Moreover, chemotherapy may be given at the same time as radiation therapy, called chemoradiation therapy, to increase the effectiveness of the radiation therapy [46].

For CRC, some targeted therapies may be used as:

3.2.1.1. Epidermal growth factor receptor (EGFR) inhibitors

Researchers have found that drugs that block EGFR may be effective for stopping or slowing the growth of CRC [47], Cetuximab [48], Panitumumab [49].

Recent studies show that cetuximab and panitumumab do not work on tumors with mutations or alterations, to a gene called rat sarcoma virus **(**RAS). It is recommended that all people with metastatic CRC who may receive an EGFR inhibitor to be tested for RAS mutation [47].

Recently, the need to use natural drugs to stop cancer has emerged. Carotenoids are the focus of study for a long time. They are a type of secondary metabolites that are extremely vital and valuable and the most diversified and widely distributed pigments on the planet [50-52].

4. Carotenoids

Carotenoids are essential components of human nutrition as they reduce the risk of developing chronic degenerative diseases like neurologic disorders (e.g. Alzheimer's disease), type 2 diabetes, age-related macular degeneration, obesity, cardiovascular diseases and other types of cancer (CRC, ovarian, breast, and cervical).

They also improve the immune system functions. They can be used as precursors of vitamin A. moreover, the composition of carotenoids is complicated and varies in both quantity and quality depending on the variety and color [50, 53-56].

Carotenoids are highly unsaturated derivatives of isoprene, which are made up of 8 isoprene units and belong to the category of tetraterpenoids containing 40 carbon atoms. Most carotenoids consist of a core chain with conjugated systems that are substituted with various cyclic and acyclic substituents. Carotenoids are distinguished by their long polyene chain which allows them to absorb light in the visible range of the spectrum from yellow to red [57-60].

Carotenoids are absorbed and accumulated in lipophilic environments. They are known as carotenes such as beta carotene and lycopene. Beta and alpha carotenes suppress the tumor formation in the colon, lungs, skin and liver, and lycopene reduces the risk of cardiovascular disease and prostate cancer [53, 55, 58, 59, 61].

Herein, this review is going to discuss some carotenoids and their effect on UC and CRC.

4.1. Lycopene

Lycopene is a phytochemical, carotenoid pigment, and red-colored pigment found in tomatoes and other red fruits such as red pepper, papaya, and watermelon. It functions as a mediator in the metabolic processes of several carotenoids in organisms that can photo-synthesized [62].

Lycopene is a polyene hydrocarbon with 13 double bonds, 11 of which are conjugated. It is an unsaturated carotenoid as shown in figure 3. They are placed in a straight line It has a chemical formula. H56 C40 Two methyl groups are inserted in the middle of the molecule. The remaining methyl groups are at the 1, 6 position. They're in the 1, 5 position next to each other. A chromophore is a structure with conjugated double bonds. The antioxidant activities result from its complex system of conjugated double bonds [63].

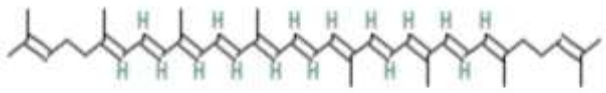

Figure 3 : Chemical structure of lycopene, [64]

In experimental studies, oral administration of lycopene in acetic acid-induced UC using male albino rats showed powerful antioxidants, anti-inflammatory, and anti-apoptotic effects. Lycopene intake leads to a significant increase in L-Malondialdehyde (L-MDA), up-regulation of NF-κB, caspase 3, and transforming growth factor-β1 (TGF-β1), and down-regulation of IL-10 and beta cell lymphoma-2 (Bcl-2) gene expression associated with a marked decrease in glutathione (GSH) level and catalase (CAT) activity [65].

Another study conducted on an acetic acid-induced UC male Wistar albino rats showed that lycopene and its colon-targeted form have a protective effect against UC as they decrease the levels of IL-1β, IL-6, NF-κB, and COX-2 compared to the conventional drug; sulfasalazine [66].

A clinical study was performed to study the effect of lycopene intake on UC symptoms. It is found that a higher intake of lycopene, lutein, and zeaxanthin is associated with lower fecal blood, mucus, and pus in individuals in the remission phase of UC but does not affect the occurrence of abdominal pain [67].

Lycopene also has anti-inflammatory effects. which results in the reduction of carcinogenesis development and progression, as well as the prevention of cell invasion, angiogenesis, and metastasis. This inhibitory effect is shown in growth factors such as insulin-like growth factor 1 (IGF-1), inhibition of receptor binding by increasing the production of insulin-like growth factor binding protein-1 and 2; angiogenesis by inhibiting matrix metalloproteinase (MMP)-2 and urokinase plasminogen activator, both of which play important roles in the metastatic process; cell cycle by inducing G1/S phase arrest and inactivation of the Ras signaling pathway; reduces the production of the anti-apoptotic protein Bcl-2 and increases the activation of caspases 3 and 8, as well as the proapoptotic molecules. Lastly, inhibition of NF-κβ and Jun N-terminal kinase (JNK) activation induces inflammation and reduces the production of TNF-, IL-1, IL-6, COX-2, and iNOS [68-71].

Two previous studies were made on dimethyl hydrazine-induced CRC rats regarding lycopene protective effect. The first one was performed on four-week-old male Wistar rats who received dietary treatment with lycopene 300 mg/kg in the basal diet; it showed a chemoprotective effect while the second one was performed on male Fisher weanling rats who were also given different concentrations of lycopene in their diet increasing concentrations of lycopene reduced the incidence of CRC [72, 73].

Another experimental study conducted on SW480 human CRC cells revealed that the mRNA expression of TNF-, IL-1, IL-6, iNOS, and COX-2 was dramatically reduced, as were the amounts of PGE2 and NO. The protein expressions of NF-κβ and JNK were significantly reduced by increasing lycopene concertation [74].

A high-carotenoid diet may also lower the development of CRC at an early stage of disease progression, according to prospective cohort studies on individuals aged 40–75 years [75-77].

4.2. Fucoxanthin

Fucoxanthin is a natural marine carotenoid obtained from brown algae and exhibits various biological activities [78]. As shown in Figure 4, it is formed of two six-membered rings connected by a polyene chain that may be accountable for its antiproliferative property [79, 80].

Fucoxanthin shows potent anti-inflammatory activity when tested in lipopolysaccharide-induced inflammation in vivo and macrophage cell lines [81]. Also, fucoxanthin induces apoptosis in leukemia cell lines and inhibits angiogenesis and breast cancer growth in vitro [82, 83].

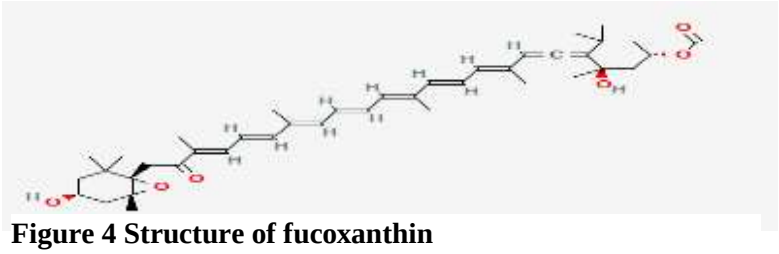

Figure 4 Structure of fucoxanthin

In dextran sulfate sodium (DSS) induced UC in mice, fucoxanthin inhibits the exacerbation of the inflammation and reduces the inflammatory markers that rise during the disease activity [84]. In UC-induced CRC in Balb/c mice fucoxanthin boosts antioxidant markers, and lowers colonic neoplasia thus, it increases the survival rate [85].

In UC-induced CRC ICR mice, the administration of 30 mg/kg fucoxanthin inhibits CRC adenocarcinoma and induces apoptosis via induction of caspase 3 [86].

In a Korean population, dietary seaweed intake inhibits CRC in patients with the dominant homozygous of rs6983267 single nucleotide polymorphism in c-MYC; an oncogene that has a role in cell growth [87].

Fucoxanthin inhibits the growth of CRC; and Caco-2 cell lines. It is also converted into fucoxanthin, the more active form, in CRC clinical specimens [88].

4.3. Beta carotene

Beta carotene is a naturally occurring retinol and a pro-vitamin as well. Beta carotene has antineoplastic properties and antioxidants [89].

Beta carotenes suppress tumor formation in the colon, lungs, skin, and liver, and lycopene reduces the risk of cardiovascular disease and prostate cancer [53, 55, 58, 59, 61].

Beta carotene has anti-inflammatory and antioxidant properties due to polyene bonds as shown in figure 5. It can play an important role in stopping the development of UC-induced CRC by modulating the microbial flora in the colon and decreasing the proinflammatory cytokines [90].

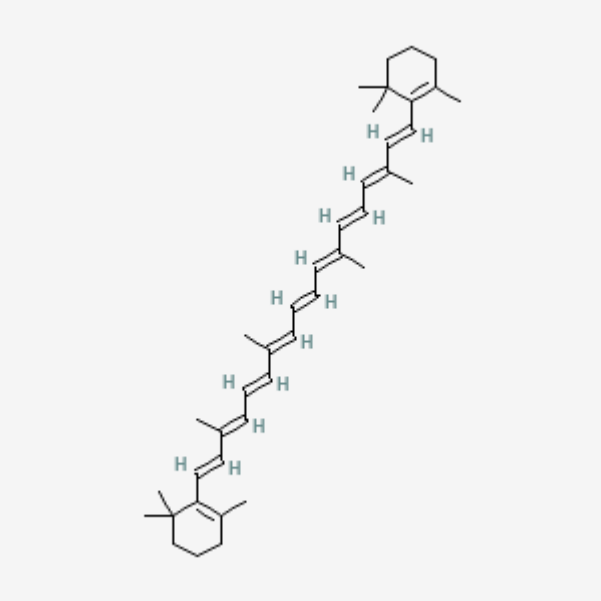

Figure 5 : Structure of beta carotene [91]

5. Conclusion

Carotenoids such as lycopene, fucoxanthin, and beta carotene have different roles in the treatment of UC and CRC as well and may be considered as one of the future medicines to be applied in the treatment of different complications of UC.

Competing interests

The authors declare they have no conflict of interest.

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Author contributions

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