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Review

Colorectal Carcinogenesis: Role of Oxidative Stress and Antioxidants

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Abstract. *One of the contributory causes of colon cancer is the negative effect of reactive oxygen species on DNA repair mechanisms. Currently, there is a growing support for the concept that oxidative stress may be an important etiological factor for carcinogenesis. The purpose of this review is to elucidate the role of oxidative stress in promoting colorectal carcinogenesis and to highlight the potential protective role of antioxidants. Several studies have documented the importance of antioxidants in countering oxidative stress and preventing colorectal carcinogenesis. However, there are conflicting data in the literature concerning its proper use in humans, since these studies did not yield definitive results and were performed mostly in vitro on cell populations, or in vivo in experimental animal models.*

Colorectal cancer (CRC) is classified as the 3rd most common malignancy worldwide as it accounts for approximately 9% of all cancer incidence worldwide, moreover it is the 4th most prevalent cause of cancer mortality (1, 2). Several pathways underlie CRC pathogenesis, however, the main 3 routes are: the chromosomal instability pathway (CIN), the microsatellite instability pathway (MSI), and the serrated pathway (3). The majority of CRCs arise from the CIN pathway, which is characterized by defects in chromosomal segregation, telomere stability, and the DNA damage response. On the other hand, MSI derives from the loss of DNA mismatch repair and is found in about 15% of all CRCs (2). Several risk factors are related to the onset and progression of colorectal cancer, such as environmental factors, physical inactivity, smoking, alcohol consumption, diet and obesity among others. A cross-talk between these known risk factors could lead to oxidative stress, with an accompanying overproduction of reactive oxygen species (ROS), that could result in mutations and promote oncogenic phenotypes (1). In CRC, the process of carcinogenesis involves complex interactions between environmental and lifestyle factors whereby multiple molecular pathways intersect to promote its occurrence. However, genetic factors play a lesser role (up to 20% of cases). Risk factors for CRC include exposure to toxins, regular consumption of alcohol, diet high in red meat and saturated fat and low in fiber and vegetables, male gender, older age, obesity, lack of physical exercise and smoking (3). Despite the multiple factors responsible for its onset, the incidence and prevalence of CRC increase more in patients with with inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD) (4, 5). For UC patients, this risk might be linked mainly to the disruption of the physiological balance in intestinal microbiota (dysbiosis). Moreover, the duration and the extent

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of the disease in the colon, as well as the cumulative effects of inflammation caused by continuous exposure of the mucosa to inflammatory stimuli are among the leading factors associated with the development of CRC in UC patients (6). However, for CD patients, this risk is associated with individual risk factors (7). Currently, it is clearly documented that any dysregulation or imbalance of the gut microbiota might lead to changes in colocytes as well as extraintestinal disease (5, 6). This disruption causes an extensive and persisting inflammatory reaction, manifested by up-regulation of an array of pro-inflammatory mediators both locally and systemically, such as; cyclooxygenase 2 (COX-2), prostaglandin E_2 (PGE_2), tumor necrosis factor α (TNF-α), nuclear factor kappa B (NFkB), and transforming growth factor β (TGFβ) among others (8-10). Persistent inflammatory reaction, in its turn, leads to the development of IBD by activating the Gut Associated Lymphoid Tissue (GALT) (4). Subsequently, the permeability and the integrity of the intestinal mucosa are altered, thus exposing colocytes to the action of pathogenic bacteria and mutagenic and carcinogenic factors (6). The process of carcinogenesis starts from dysplastic colocytes that begin to proliferate, giving rise to adenomatous polyps. If these polyps are not detected and removed in time, cancerised polyps and finally colorectal cancer arise (2). This sequence of chronic inflammation - dysplasia - adenoma - carcinoma was well described in 1988 by Vogelstein (11), who also reported the various mutations involved in the pathogeneisis of CRC (Figure 1) (4).

In addition, the transition from adenoma to carcinoma requires a set of molecular events such as the activation of proto-oncogenes, inhibition of tumor suppressors, destruction of the cellular matrix, DNA mutations and changes in DNA methylation state (12). These DNA mutations are mostly caused by oxidative stress, another important factor that is a result ROS (1, 13). When they are not counterbalanced by the antioxidant defenses of the cell, ROS cause an oxidative stress and oxidative damage to the cell. This event may cause DNA damage with subsequent mutations and chromosome instability that, in turn, may lead to cancer (1, 3).

Role of Oxidative Stress

ROS, such as hydrogen peroxide, hydroxyl radical, superoxide anion and peroxynitrite are derived from the incomplete reduction of oxygen, as byproducts of normal energy metabolism (13, 14). They are continuously produced in aerobic organisms (14) from both endogenous, such as mitochondria, cytochrome *P450* metabolism, peroxisomes or inflammatory cell activation, as well as exogenous sources (14). Production of ROS is increased by exposure to toxins, smoking, stress and inflammation caused by metabolic diseases, diet, lifestyle factors and dysbiosis (16). It has been estimated that one human cell is exposed to approximately 1.5×10^5 oxidative hits a day (15). These reactive species may react with biomolecules, such as lipids, carbohydrates, proteins and nucleic acids, thereby, interfering with cell function (14). As a result damage may occur in the sequence of nucleotides causing DNA strand breaks, oxidation of purine and pyrimidine bases, genetic instability (13), and alterations in DNA methylation resulting in chromosomal instability and aneuploidy. This resulting oxidative damage is the first step involved in mutagenesis, carcinogenesis and aging (3). The most common oxidative DNA damage caused by ROS is modification of the GC base pair, with subsequent base substitutions, deletions and insertions (Figure 2) (13).

Another type of mutation associated with oxidative stress and also present in CRC is DNA microsatellite instability (MSI), which contributes to incorrect DNA repair mechanisms during replication. MSI occurs when germline or sporadic mutations in mismatch repair (MMR) genes allow for replication errors or instability in repeat DNA sequences. Microsatellite instability is classified as high frequency (MSI - H) and low frequency (MSI - L), based on the percentage of the loci that show instability. Studies have shown that oxidative stress deactivates DNA repair systems, causing MSI - L and development of CRC in patients with UC (1, 17). Moreover, after the onset of cancer, ROS stimulates proliferation and survival of cancer cells by promoting oncogenic phenotypes (1) through the activation of various transcription factors (13).

Recently, the beneficial role of antioxidants found in food or dietary supplements, in colorectal carcinogenesis has become a topic of major interest. They exert their effects by minimizing the genotoxic damage caused by the accumulation of ROS, as well as by slowing cancer progression. In this capacity, antioxidants would be acting as long term chemopreventive agents (13-17).

Antioxidants

Antioxidants are a group of substances that neutralize ROS. They are also involved in several metabolic and molecular processes implicated in the growth and invasiveness of tumor cells (18, 19). Opposing oxidative stress by increasing antioxidant activity is a potentially effective means of delaying the harmful effects of ROS. For this reason, there is a growing interest in recent years focused on the assessment of the source, action, and potential health benefits of dietary antioxidants (15).

The main available antioxidants are: polyphenols, tocopherols, carotenoids, curcumin and vitamin C (Table I).

Polyphenols. Polyphenols represent a broader class of antioxidants and are found mostly in fruit, vegetables, tea, wine, coffee and cereals. In plants, they are present in glycosylated, esterified or polymerized form. Once ingested,

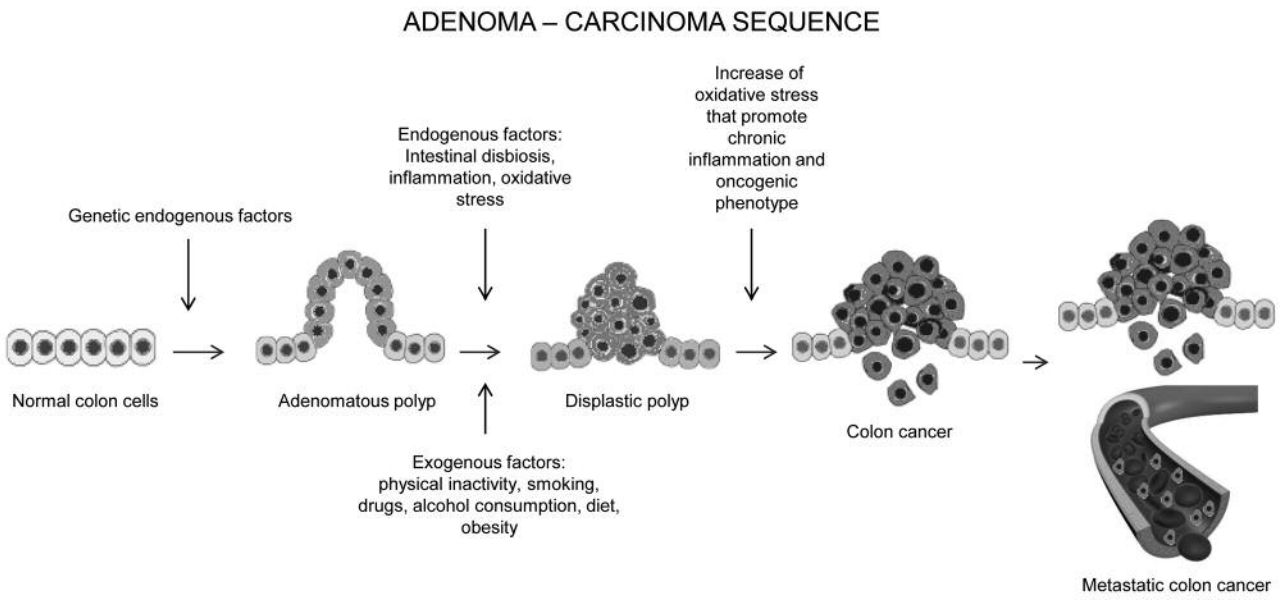

Figure 1. *Adenoma–carcinoma sequence. The sequence of facts that turn an adenomatous polyp into colorectal cancer. The transformation takes place over a period of about ten years and is attributable to a set of mutations that are accumulating in the cell.*

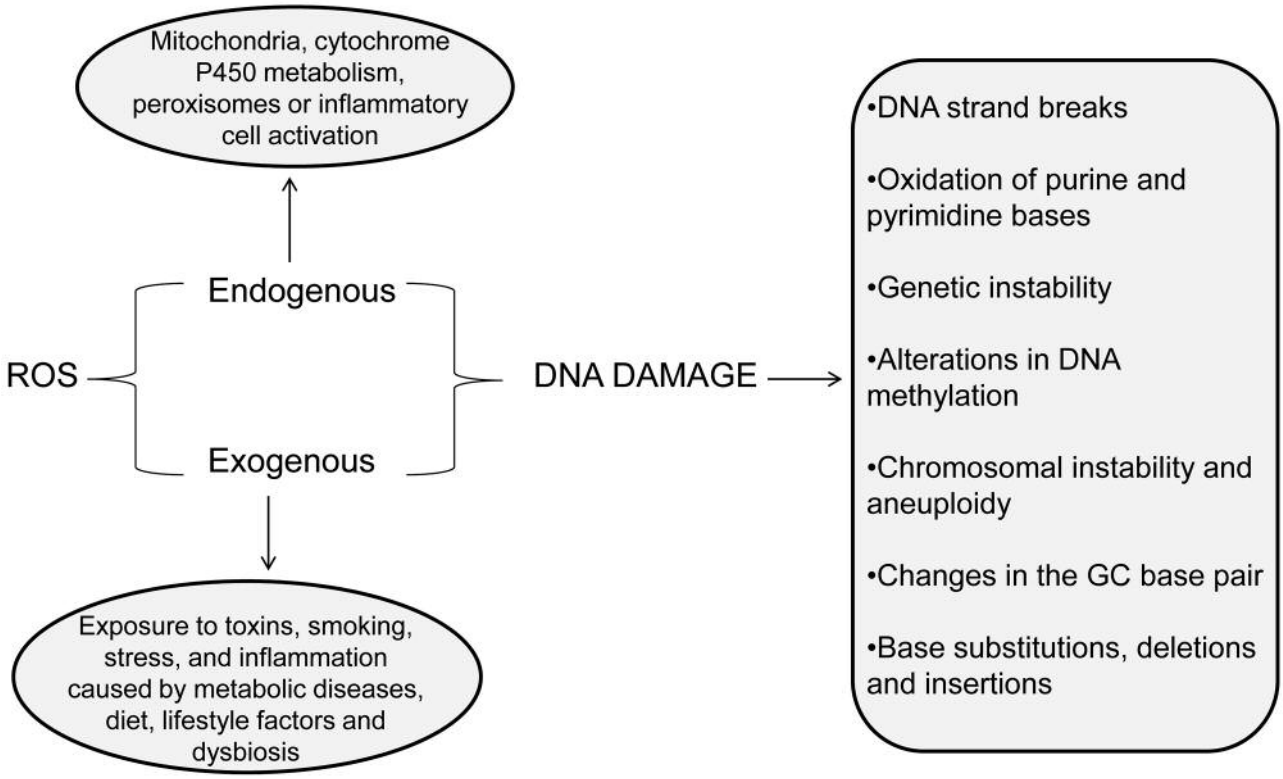

Figure 2. *Effects of ROS on DNA. ROS are continuously generated from both endogenous sources as well as exogenous substances. The main DNA damages produced by ROS are DNA strand breaks, genetic instability, changes in GC base pair and other.*

Table I. *Main available antioxidants.*

Type of antioxidants	Where they are found	Potential beneficial effects
Polyphenols	Fruit, vegetables, tea, wine, coffee and cereals	Anti-tumoral effect, modulation of the immune system, reduction of intestinal inflammation.
Tocopherols	Vegetable oil, soybean, nuts and corn	Countering the action of ROS, prevention of the formation of cell colonies, reduction of inflammation.
Carotenoids	Carrots, oranges, tangerines, tomatoes, spinach and broccoli	Anti-tumoral activity, modulation of the migration and invasiveness of colorectal cancer cells.
Curcumin	Oriental spice, frequently consumed in Indian, Pakistanian and Thai cooking	Inhibition of tumor initiation, promotion, invasion and metastasis, involvement in the modulation of DNA methylation.
Vitamin C	Fresh vegetables and fruit (as lemon, strawberry, spinach, orange)	Reducing capacity, down-regulation of metastasis, induction of apoptosis.

Table II. *Subclasses of polyphenols.*

Type of polyphenols	Where they are found	Potential beneficial effects
Quercetin	Fruit, vegetables, tea and wine	Inhibition of tumorigenesis through antioxidant, anti-inflammatory, antiproliferative, and pro-apoptotic mechanisms.
Anthocyanins	Red, blue and purple fruit as blueberries, strawberries and raspberries	Anti-aging and anti-free radical effects, inhibition of tumor growth, reduction of oxidative stress and down-regulation of inflammatory mediator expression.
Catechins	Green tea (*Camelia sinensis*)	Suppression of cancer stem cells, potent anti-oxidant activity.
Resveratrol	Red wine and grapes	Anti-inflammatory and antioxidant effects, inhibition of cell proliferation, induction of apoptotic mechanisms.

polyphenols undergo a set of changes both at the level of the small intestine and colon, where 90-95 % of the absorption takes place. Due to the activity of the intestinal microbiota, dietary polyphenols are fragmented into easily absorbed phenolic acids that are responsible for the beneficial effects (20). Currently, it is estimated that 500-1,000 different microbial species inhabit the gastrointestinal tract, reaching the highest concentrations in the colon (up to 10^{12} cells per gram of faeces). However, only a few bacterial species (*e.g.* *Escherichia coli*, *Bifidobacterium* sp., *Lactobacillus* sp., *Bacteroides* sp., *Eubacterium* sp.) catalyzing the metabolism of phenolics have been identified so far. Consequently, apart from the inter-individual variation in daily intake of polyphenols, inter-individual differences in the composition of the gut microbiota might lead to differences in the bioavailability and bioefficacy of polyphenols and their metabolites (20-23). Some of the beneficial effects of polyphenols on intestinal microbiota are reinforcement of the tight junctions between intestinal mucosal cells, an anti-tumoral effect, and modulation of the immune system resulting in an anti-inflammatory effect (21, 27). Polyphenols exert their effects through different mechanisms, such as decrease of cancer cell proliferation, apoptosis induction, reduction of angiogenesis and inflammation (25) and inhibition of specific signaling pathways such as the Wnt/β – catenin pathway (26, 27). Some of the most common polyphenols are quercetin, anthocyanins, catechins, and resveratrol (Table II) (21, 24, 27, 28).

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the major dietary flavonoids and polyphenols found in several fruit, vegetables, and beverages such as tea and wine. This nutraceutical is known as phytoestrogen for its molecular similarity with the 17β-Estrogen. It has been shown that quercetin plays a role in inhibiting tumorigenesis in colon cells through antioxidant, anti-inflammatory, antiproliferative and pro-apoptotic mechanisms (27). It is able to inhibit cell proliferation of CRC *in vitro*, by modulating the activity and expression of the estrogen receptor ERβ (28, 29). On HT-29 cells, quercetin decreased significantly cell viability, induced cell-cycle arrest in the G_1 phase, and increased the expression of apoptosis related proteins, such as AMPK, p53, and p2 (30).

Table III. *Subclasses of tocopherols*.

Type of tocopherols	Where they are found	Potential beneficial effects
δ-Tocopherol	Vegetable oil (sesame oil, canola oil, sunflower oil)	Induction of apoptosis and prevention of cell colony formation.
γ-Tocopherol	Vegetable oil (sesame oil, canola oil, sunflower oil)	Reduction of inflammation and consequently, reduction of the risk of cancer progression.

Table IV. *Subclasses of carotenoids with anticancer effects*.

Type of tocopherols	Where they are found	Potential beneficial effects
α- and β-Carotene	Orange foods such as carrots	β-Carotene, in the form of retinol: Inhibition of tumor cell invasiveness and ability to migrate through the extracellular matrix
Lycopene	Tomatoes	Inhibition of growth factors, angiogenesis, and apoptosis

Anthocyanins, (Greek anthos=flower and kyanos=blue) are water-soluble pigments responsible for the red, blue and purple color of some fruit (such as blueberries, strawberries and raspberries). In plant cells, they are present in vacuoles in the form of various sized granules. Numerous recent studies are shedding light on these pigments as dietary components with preventive impact on cancer as well as effective, cheap and safe anticancer supplements. They also seem to have anti-aging and anti-free radical effects (31-33). Furthermore, anthocyanins derived from sweet potato were shown to inhibit the development of CRC (34). This compound was able to induce anti-proliferative and apoptotic mechanisms as well as cell cycle arrest both *in vivo* and *in vitro* (31). Finally, anthocyanins present in black raspberry are able to inhibit the growth of cancer cells *in vitro* through the demethylation of tumor suppressor genes (32).

Catechins, found predominantly in green tea (*Camelia sinensis*), are regularly consumed in many Asian countries as a traditional medicine with multiple health benefits to improve blood circulation, wound healing, and digestion. Its principal extract Epigallocatechin-3-gallate (EGCG) has been shown to be a potent anti-oxidant which acts through chelating metal ions (26). Recently, EGCG has been shown to suppress cancer stem cells (CSCs), which are a small subset of cells playing a major role in chemoresistance and tumor recurrence. By targeting CSCs, EGCG was able to enhance fluorouracil (5-FU) sensitivity in chemoresistant CRC. Thus, the use of this natural product may provide a safe and effective adjunct approach in overcoming conventional chemotherapy resistance in colorectal carcinogenesis (35).

Resveratrol is a compound found in various foods including red wine and grapes (especially the peel of the grape berries). It has been shown that resveratrol has anti-inflammatory and antioxidant effects. It acts mainly through the inhibition of cell proliferation, induction of apoptotic mechanisms, and down-regulation of K-ras (12).

Tocopherols. Tocopherols, better known as vitamin E, are a group of fat-soluble compounds found in foods such as vegetable oil (*i.e.* sesame oil, canola oil, and sunflower oil), soybean, nuts and corn (25). Structurally, they occur in α, β, γ and δ –form, determined by the position and number of methyl groups on the chromanol ring (25, 36). Their antioxidant activity is expressed at the level of cell membrane by countering the action of ROS on its lipid bilayer, thus playing a protective role against ROS-induced carcinogenesis (25). Particularly δ-tocopherol has the highest inhibitory activity on CRC cells among the other family members, inducing apoptosis and preventing the formation of cell colonies (37, 38). Moreover, γ-tocopherol reduced inflammation in a moderate colitis and, consequently, reduced the risk of progression to cancer (36). Furthermore, γ and δ-tocopherols were able to inhibit carcinogenesis in a mouse model of colorectal cancer by reducing the inflammatory reaction and preventing the formation of dysplasia and aberrations (Table III) (25).

In brief, metabolites resulting from the processing of intestinal tocopherols have anti-inflammatory effects. These end-products act through the inhibition of COX and lipoxygenase, therefore, they might be useful in the reduction of chronic inflammation in IBD and subsequently CRC prevention (36).

Carotenoids. Carotenoids are a group of yellow, orange, and red fat-soluble pigments, that are divided into two main groups: Those with pro-vitamin activities (vitamin A) that include α- and β-carotenes (found mainly in orange foods such as carrots) and β-cryptoxanthin (found in citrus foods such as oranges and tangerines), and those without pro-vitamin activities, which include lycopene (present in large quantities in tomatoes), lutein, and zeaxanthin (found in green foods such as spinach and broccoli) (39). Numerous studies have demonstrated the antioxidant activity of carotenoids and their potential role in reducing the risk of developing colon cancer. β-Carotene, once ingested, undergoes several enzymatic processes that transform it firstly into retinaldehyde and subsequently retinol (also known as vitamin A). Retinol is able to inhibit the invasiveness of tumor cells and their ability to migrate through the extracellular matrix. An increase of dietary β-carotene intake might have an antitumor effect due to the ability of β-carotene to modulate the migration and invasiveness of CRC cells. β-Carotene is the substrate of the enzyme β-carotene 15,15'-monooxygenase, which is inhibited in preneoplastic intestine leading to an increased expression of matrix metalloproteinases and subsequently an increased tumor invasiveness. β-Carotene has been shown to up-regulate the inhibited enzyme in colon cancer cells, *in vitro*, thus presenting antitumor effects (40, 41) (Table IV). Among other carotenoids, lycopene also exerts anti-inflammatory activity resulting in the suppression of inflammation-associated promotion and progression of carcinogenesis, inhibition of cell invasion, angiogenesis and metastasis (39). However, conflicting data concerning carotenoids exist, for example studies on the association between increased consumption of dietary carotenoids and reduced risk of CRC have not yielded any significant results (40-42).

Curcumin. Curcumin, one of the active ingredients in turmeric (Curcuma longa), is a common oriental spice that gives the curry powder its yellowish color. It is more frequently consumed in Indian, Pakistanian and Thai cooking. Curcumin exerts a powerful anti-inflammatory activity by interacting with different molecular mechanisms such as transcription factors, regulatory proteins, and enzymes in addition to antifungal, antibacterial and anticancer properties. Curcumin acts at several stages of cancer development. It inhibits tumor initiation, promotion, invasion and metastasis as revealed in several studies (2, 3). This antioxidant is also involved in the modulation of DNA methylation in colon cancer cells and thus seems to have chemopreventive effects. For this reason, this nutraceutical is currently the focus of numerous studies shedding light on its role in various chronic conditions including autoimmune, cardiovascular, neurological, and most importantly by being a promising chemopreventive natural agent with numerous targets and no reported adverse or toxic effects (2, 3).

Vitamin C. Vitamin C (ascorbic acid) is an acidic polyol with six carbon atoms and α-keto mycolactone. It is mainly found in fresh vegetables and fruit. The antioxidant ability of vitamin C is reflected by its reducing capacity, which means it can directly and rapidly react with the superoxide ion O_2^- and singlet oxygen through dehydrogenation. Its serum concentration in healthy humans is 48.3-79.5 μmol/l (43). In recent years, a large number of basic and clinical studies showed that vitamin C plays an important role in a series of diseases caused by oxidative stress, such as cardiovascular disease and cancer. Vitamin C was also shown to have an effective role in the treatment and prevention of cancer. The exact pathways through which this molecule exerts its antitumorigenic effect are not well defined. However, the main mechanisms are the induction of apoptosis *via* the disruption of mitochondrial membrane potential, as well as the suppression of cancer cell proliferation through cell-cycle arrest at G_1 stage, leading to the modulation of the activity of p53-$p21^{Waf1/Cip1}$ and CDK2 (44). Vitamin C has been shown to have an antitumor activity, as the exposure to high levels of vitamin C led to cell death of human CRC cells harboring *KRAS* or *BRAF* mutations, *in vitro*. In particular, it appears that oxidized form of vitamin C, dehydroascorbate (DHA), has selective toxicity to cancer cells through redox homeostasis desruption, though the exact mechanism of action remains unclear (45). However, it is possible to hypothesize that since more than half of human CRCs carry either *KRAS* or *,0* mutations, and are often refractory to approved targeted therapies, Vitamin C might be a promising therapeutic agent in colorectal carcinogenesis (44, 45).

Conclusion

It is well-documented that one of the contributory causes of colon cancer is the effect of oxidative stress on the DNA sequence resulting in the eventual progression of adenoma to carcinoma. Studies on the action of antioxidants on oxidative stress and on CRC are not always in agreement, however, the positive health effects of antioxidants on CRC have always been implicated. Consequently, antioxidants are being consumed on almost routine basis in patients with CRC. This is despite the fact that no direct human data have been confirmed. However, data emanating from *in vitro* studies and from animal models are encouraging in decreasing the rate of progression of CRC. Therefore, larger studies involving CRC patients are required to further elucidate the importance of dietary antioxidants on colorectal carcinogenesis. In brief, at this point, the use of antioxidants could be recommended and justified to patients with history of IBD and CRC.

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