Chemoprevention with Phytonutrients and Microalgae Products in Chronic Inflammation and Colon Cancer

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Abstract: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder caused by deregulated immune responses in a genetically predisposed individual. This is a complex process mediated by cytokines, chemokines, adhesion molecules, cytoplasmic nuclear receptors, among others. Recent data support a participation of the endoplasmic reticulum (ER) stress and mitochondrial dysfunctions in IBD. Moreover, now it is evident that chronic degenerative pathologies, including IBD, share comparable disease mechanisms at the cellular level with alteration of the autophagy mechanisms.

Mounting evidence suggests that the risk of developing colorectal cancer (CRC) is dramatically increased in patients with chronic inflammatory disease. Chronic inflammation in IBD exposes these patients to a number of signals known to have tumorigenic effects including nuclear factor kappa B (NF-κB) activation, proinflammatory cytokines and prostaglandins release and reactive oxygen species (ROS) production.

Chemoprevention consists in the use of drugs, vitamins, or nutritional supplements to reduce the risk of developing, or having a recurrence of cancer. Numerous in vitro and animal studies have established the potential colon cancer chemopreventive properties of phytochemicals derived from both plants (curcumin, resveratrol, epigallocatechin gallate, quercetin or genistein) and substances from marine environment, including microalgae species and their products. This review summarizes the mechanisms by which these naturally occurring compounds may mediate chemopreventive effects on cancer. These actions include induction of cell cycle arrest and apoptosis, inhibition of cell proliferation, stimulation of antimetastatic and antiangiogenic responses and increased antioxidant and anti-inflammatory activity.

Keywords: Gut, immunology, chronic inflammation, colon cancer, inflammatory bowel disease, chemoprevention, phytonutrients, microalgae.

1. INFLAMMATORY BOWEL DISEASE: IMMUNE RESPONSES AND MOLECULAR PATHWAYS IMPLICATED

The incidence of IBD continues to rise, mainly in high-incidence areas (western countries), although both incidence and prevalence are also increasing in historically low-incidence areas such as Latin America, India East or Asia. Factors associated with this “westernization” may be conditioning the expression of these pathologies, and the increase of the incidence among migrants from low- to high-incidence regions in just one generation suggests a strong environmental influence [1].

The hallmark of IBD, including ulcerative colitis (UC) and Crohn’s disease (CD), is chronic uncontrolled inflammation of the intestinal mucosa, which can affect any part of the gastrointestinal tract, with presence of structure alterations and superficial or transmural granulomatous infiltration [2]. IBD is associated with increased permeability of the intestinal epithelial lining resulting in continuous stimulation of the mucosal immune system. Luminal bacteria appear to further intensify the permeability defect, establishing a self-sustaining cycle of mucosal inflammation. Intestinal epithelial cells have developed control mechanisms that organize the activation of the intestinal immune system. However, under pathological conditions, bacterial products are able to cross the mucosal barrier and come into the mucosa generating a classic immune response [2, 3].

The traditional paradigm for the IBD pathogenesis was that cells from the adaptive immune system are also the mediators of intestinal inflammation (Fig. 1). However, now the participation of the innate immune system in IBD is accepted [4-6]. In this sense, the intestinal epithelium is believed to contribute to innate immunity and to the relative sterility of the mucosal surface, playing an active role in the maintenance of the mucosal immune homeostasis [7]. Likewise, the intestinal epithelium appears to act as a “gatekeeper” that regulates the quality (type) and quantity (number) of leukocytes migrating from the intravascular to the interstitial space [8]. This is a complex process mediated by cytokines, chemokines and adhesion molecules. After exposure to the abundant intestinal bacterial antigens or environmental factors, innate immune cells in intestinal mucosa are activated, leading to the overproduction of proinflammatory cytokines. Recently, the interleukin (IL)-23/IL-12 pathway has become the subject of intensive study and the Th helper type 1 (Th1) cells, driven by IL-12, and IL-17-producing Th helper (Th17) cells, driven by IL-23, have been demonstrated to play an important role in IBD [9]. The Th17 pathway genes are shared between CD and UC, while others are IBD subtype-specific including autophagy genes, or epithelial barrier genes [10, 11] have demonstrated that the IL-23 receptor is vital for the maintenance of many types of CD-T cells which provide early adaptive immune responses to damage. These IL-17 producing effector T cells are crucial for protection against intercellular pathogens and for organ-specific inflammation; the therapeutic disruption of the IL-23 pathway suggests the control of auto-immune inflammation without impairing systemic immunity [12].

Many receptors are implicated in the immunopathogenesis of IBD and those located on the intestinal mucosal surface constitute an immunological barrier that is in continuous contact with a variety of commensals. Structurally distinct families of pattern recognition receptors (PRRs) are pivotal to the control of intestinal mucosal homeostasis [13]. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-1 (NOD-1)-like receptors, both interconnected and coordinated through many signals pathways, provide an integrated system to recognize microbes and microbial molecules and to control antimicrobial effectors pathways and adaptive immune responses.

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sis. Along these lines, TLR-2 recognizes a vast array of microbial imbalance or dysbiosis, contribute to disease pathogenesis, suggesting the possibility that abnormal bacterial sensing, immune responses. Several studies have described the low expression, and prostaglandin E2 (PGE2) production. The stimulation of NF-kB signaling pathway induces the expression of a number of genes: the angiogenic factor named vascular endothelial growth factor (VEGF), the antiapoptotic factor Bcl-2, and the proliferation factor cyclin D1. Inflammatory regulators also act in a feedback loop to modify regulatory systems including AMP-activated protein kinase (AMPK) and sirtuin deacetylase enzyme (SIRT1) -1, and to weaken p53 activity. Finally, the vicious circuitry of inflammation and cancer modifies apoptosis and autophagy and promotes cell cycle progression, invasion, and angiogenesis. Endoplasmic reticulum (ER) stress and mitochondrial dysfunctions in epithelial cells are also disease-conditioning situations in IBD. The UPR/IRE1α/XBP1 pathway results in induction of autophagy. Phytochemicals and phytonutrients have been reported to directly modulate various molecular signals transduction pathways that are known to induce cancer cell death or to inhibit cancer cell proliferation. However, many of the specific molecular and cellular targets need to be confirmed.

In healthy people, normal PRR signaling protects intestinal barrier integrity and confers commensal tolerance, and different studies suggest that this kind of signalling exerts several important cytoprotective responses in the intestine epithelium, including barrier preservation, inhibition of apoptosis and inflammation, wound repair and regeneration, and autophagy control [13]. Autophagy, traditionally considered as simple as a degradation mechanism, is now believed to have numerous functions and to play complex roles in human diseases, including IBD [14]. The progress made by scientific programs such as the human genome project and genotyping technologies, have made the discovery of susceptibility loci for IBD that are shared between UC and CD, but also a number of loci that are disease-specific [15]. Association between two genes, the autophagy-related 16-like 1 gene (ATG16L1) and immunity-related GTPase family, M (IRGM), and CD was identified by a genome study and by a wide single nucleotide polymorphisms- SNP study [16, 17].

Aberrant PRR signaling, occurred in disease, leads to deleterious tissue injury associated with chronic inflammatory and autoimmune responses. Several studies have described the low expression of TLR-4 in the normal colonic mucus and the upregulation in UC [18], suggesting the possibility that abnormal bacterial sensing, microbial imbalance or dysbiosis, contribute to disease pathogenesis. Along these lines, TLR-2 recognizes a vast array of microbial components and is involved in different models of IBD [19], however TLRs do not discriminate between pathogenic and nonpathogenic microorganisms (commensal), which is important for understanding innate signalling [20]. Concerning NOD-1-like receptors (NLRs), they are expressed not only by dendritic cells [21], but also by Paneth cells and macrophages [22] and like TLRs, they do not differentiate between pathogenic microorganisms and commensal flora [20]. The first innate receptor strongly linked to the development of chronic intestinal inflammation in a subset of CD patients is the nucleotide-binding oligomerization domain-containing protein 2 (NOD2), also known as caspase recruitment domain-containing protein 15 (CARD15) or also as inflammatory bowel disease protein 1 (IBD1) NOD2/CARD15 [23, 24]. NOD2 mutations are associated with an increased risk for CD, which suggests that the deregulated recognition of intestinal microbes leads to disease in a genetically predisposed individual. Recently, two independent groups have linked NOD2 and autophagy [25, 26]: NOD2 stimulation induces autophagy in dendritic cells and requires ATG5, ATG7 and ATG16L1. NOD2-mediated autophagy affects bacterial handling and antigen presentation in dendritic cells and mutant NOD2 is retained in the cytosol and therefore fails to bring ATG16L1 to the plasma membrane, impairing autophagy targeting of bacteria. Autophagy has been identified as a key process in host resistance to bacterial infection, although little is known about the
steps by which pathogens manipulate the cell to evade the autophagy pathway. The connection between autophagy and IBD development can exist on multiple levels, including intestinal homeostasis, bacterial clearance, cytokine production, and Paneth cell functions [15], whereas some genetic alterations of autophagy promote the development of IBD. In addition, other processes related to IBD pathology (responses to pathogens, oxidative damage and other stresses) would be presumably altered by malfunction of the autophagic process.

On the other hand, upon contact of microbial components with both NOD2 and TLR, NF-kB signaling pathway stimulates the expression of multiple molecules relevant to the pathogenesis of various diseases including IBD and CRC [27, 28]. NF-kB signaling pathway is a complex network that regulates a cellular pathway involved in the expression of a wide variety of genes that play critical roles in immune responses [29]. NF-kB is regulated by the IkB family, with seven IkB members including IkBa, IkBAl, IkBBl, IkBBr, IkBa, Bcl-3 and the precursor proteins p100 and p105. Briefly, following stimulation with various inflammatory stimuli, such as certain members of the tumor necrosis factor alpha (TNF-α) cytokine family, IL-1, TLR ligands, and the p50 subunit mostly, which translocate to the nucleus and activates the transcription of various target genes [30]. The result is the increase production of proinflammatory molecules during active IBD, including those encoding cytokines such as IL-1, IL-2, IL-6, IL-12, and TNF-α [31]. These cytokines are primarily secreted by monocytes and macrophages upon activation and then induce intestinal macrophages, neutrophils, fibroblasts and smooth-muscle cells to produce prostanoids, proteases and many other mediators of inflammatory tissue responses, and promote the production of other chemotactic cytokines affecting innate as well as acquired immune response at mucosal sites [32].

In response to NF-kB activation, commensal bacteria dampen inflammation via nucleaseby the redistribution of peroxisome proliferator-activated receptor (PPAR-γ), a member of the nuclear receptor group of transcription factors. PPAR-γ is highly expressed in the intestinal epithelium, immune cells and adipocytes, and regulates a number of genes participating in metabolism, proliferation, signal transduction and cellular motility. The role of PPAR-γ in the immune response is through its ability to down-modulate the expression of inflammatory cytokines such as IL-1β, TNF-α, and interferon-gamma (IFN-γ) and also to direct immune cell differentiation towards anti-inflammatory phenotypes [33]. In addition, other mechanisms involved in the anti-inflammatory effects of PPAR-γ ligands include modulation of NF-kB, c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) signalling pathways [34] (Fig. 2). PPAR-γ activation contributes to the maintenance of intestinal homeostasis in several experimental assays. A recent in vivo study by Guri et al. [35] investigated the underlying mechanisms by which the deletion of PPAR-γ in intestinal epithelial cells modulates the severity of experimental IBD, immune cell distribution and global gene expression. These authors observed that PPAR-γ expression is required for preventing colonic inflammatory lesions, up-regulating lysosomal pathway genes and increasing the production of the anti-inflammatory cytokine IL-10. In a different experimental model of IBD, activation of PPAR-γ by different agonists suppressed gut inflammatory lesions, weight loss and inflammatory mediators expression [36-38]. Most notably, the PPAR-γ agonist rosiglitazone showed therapeutic efficacy in humans with UC, although this molecule and other drugs belonging to the thiazolidinedione class of anti-diabetic drugs, are unlikely to be adopted for the treatment of IBD because of their side effects [39].

It is now evident that chronic degenerative disorders, such as type 2 diabetes or IBD, share comparable disease mechanisms at cellular level, including ER and mitochondrial dysfunctions, with inflammatory processes as a key disease-conditioning situation in different tissues [40, 41]. Stress in mitochondria, or in the ER independently, causes cell death, but these process may be also connected: it has been reported that ER stress causes mitochondrial dysfunction via p53-upregulated modulator of apoptosis (PUMA) and tumor necrosis factor receptor-associated protein 1 (TRAP1), located in the mitochondria and associated with the unfolded protein response (UPR) in the ER [42]. Genetic and environmental factors can affect ER stress in the intestinal epithelium and consequently inflammation [43]; genetic factors include either primary or secondary ER stress and environmental factors include bacteria, diet or drugs. The hypothesis that ER and mitochondria share common mechanisms in triggering the UPR and a protective signalling pathway from the ER to the nucleus controls cell-stress-response caused by unfolded and/or misfolded proteins. Accumulation of unfolded or misfolded proteins in the ER results in increased chaperone expression, translational arrest and induction of autophagy and UPR signaling is mainly driven by inositol-requiring endoplasmic reticulum-to-nucleus signaling protein 1α (IRE1α), X-box-binding protein 1 (XBP1) pathway [44]. IRE1α is a transmembrane kinase/endoribonuclease, which initiates the non-conventional splicing of the messenger RNA (mRNA) encoding the key transcription activator XBP1 which is a key component of the ER stress response and is required for the differentiation and function of certain secretory epithelial cells [45, 46]. IRE1α is ubiquitous, whereas IRE1β is specifically expressed in the intestinal epithelium. IRE1α exhibits both endoribonuclease activity, with XBP1 being the only known substrate, and kinase activity that engages both JNK and classical NF-kB pathways. XBP1 deletion causes ER stress in the epithelium, enteritis, increased susceptibility to dextran sodium sulfate (DSS) colitis, lacks of Paneth cells in the intestinal epithelia, and decreases cryp bac tericidal function, among others.

The full understanding of the different immunological mechanisms implicated in the development and perpetuation of chronic inflammatory diseases, such as IBD, is very important as therapeutic interventions are subject to these mechanisms. In this way, treatments could be customized for each specific group or subgroup of patients.

2. INTESTINAL CANCER AS A CONSEQUENCE OF CHRONIC INFLAMMATORY DISORDER

At present, reasons for the elevated cancer risk in IBD patients are not clear. Genetic predisposition and data from familial cases of intestinal cancers could indicate their connections, although it is not clear which heritable genetic factors contribute to increased CRC risk in IBD.

Since Hinton et al. [47] reported in 1966 that patients with ulcerous colitis were at greater risk of developing CRC, many papers have reported that the length of the disease, its extent and association with other inflammatory diseases such as sclerosant colangitis, and anti-inflammatory treatment are factors that can decrease inflammation in an advantageous role, at least, in carcinogenesis [48, 49]. Intestinal neoplasias, originated under inflammatory conditions, have been the object of numerous clinical, anatomopathological, genetic and molecular studies in both humans and animals. The association between IBD and elevated risk for CRC is clear; however, there are some debates about whether CD possesses a similar risk [50]. Earlier studies did not find a significant increase in the risk, although several other studies support the association between CD and cancer. Therefore, although most of the knowledge about colon cancer from chronic intestinal conditions comes from UC evidence, the data suggest that both of these conditions confer increased intestinal cancer risk.

Experimental models in animals have been tested, but only a few are applicable in the study of the inflammation-dysplasia-cancer sequence, which is evident in histological studies of the affected intestinal mucosa [51, 52]. All histological studies are based on the histological classification proposed by Riddle et al. [53] and Pascal [54]: i) Undefined for dysplasia/probably negative.
ii) Undefined-defined for dysplasia/probably positive. iii) Low grade dysplasia. iv) High grade dysplasia. v) Carcinoma. However, the identification of dysplasia in intestinal inflammatory diseases represents a huge challenge for both clinicians and pathologists, so a clear diagnosis of dysplasia in IBD is not always possible. Possible markers, such as p53 and alpha-methylacyl coenzyme, have been used. The combination of these two markers is positive in 75.8% for cancers and 30.3% for undefined biopsies for dysplasia, while only in 0.6% for non-neoplastic epithelium.

The suspect lesions can be visible macroscopically or only microscopically. Bird and Good [55], in 1987, described focal points of aberrant crypts (AC) such as preneoplastic lesions in rodents treated with carcinogen. The AC can be high or flat lesions: “high AC” are microscopical large lesions that raise above the surrounding epithelium, presenting a round, elongated, open lights. “Flat AC” do not raise above the epithelium, showing a brilliant methylene blue and presenting small or slightly enlarged as well as compressed open lights. Their detection results from the combination of methylene blue staining and transillumination [55]. &-catenin and cycline D1 expression has been studied in both, high and flat ACs; while &-catenin is found in the cytoplasm of flat lesions, it moves to the cytoplasm and nucleus in polypoidal lesions. Thus, inflammation seems to play an important role in the dysplasia-cancer sequence both in flat lesions and in mass, while the translocation of &-catenin to the cytoplasm and nucleus is an early event that occurs in polypoidal lesions [56].

Several lines of evidence implicate chronic intestinal inflammation as a key predisposing factor to modulate tumorigenesis. The relationship and mechanisms through which infection and inflammation increase cancer risk and promote tumor development have been recently the object of important revisions [57, 48]. Chronic inflammation and repeated events of inflammatory relapse in IBD expose a number of alterations known to have procarcinogenic effects. Carcinogenesis, divided into three phases (initiation, promotion and progression), is influenced by different inflammatory mediators (Fig. 1).

The contribution of the inducible isoform of cyclooxygenase (COX-2) to carcinogenesis is well established. COX-2 can activate procarcinogens and indirectly increase free-radical production. The relationship between ROS and COX-2 expression has been addressed in a recent study which demonstrated that the chemopreventive sulindac and nitric oxide-donating aspirin (NO-ASA) generate ROS to induce COX-2 expression, which can be abolished by two antioxidants and an inhibitor of NADPH oxidase [58]. Recent data implicate COX-2 production downstream of TLR4 activation in the development of inflammation-associated colorectal neoplasia [48, 59]. Activation of TLR4 initiates a signaling cascade that culminates in NF-kB activation and subsequent transcription of a number of proinflammatory mediators, including COX-2. Whether NF-kB is required for ROS-induced COX-2 expression, however, needs further elucidation. Nonsteroidal anti-inflammatory drugs (NSAID) may inhibit the development of gastrointestinal cancers through inhibition of COX-2 activity. Nevertheless, COX-2-independent mechanisms also contribute significantly to the chemopreventive effects of NSAID. In any case, the available data reinforce the role of COX-2 in chronic inflammation and in the development of CRC [48].

Fig. (2). The mechanisms by which peroxisome proliferator-activated receptor (PPAR)-&gamm; exerts its anti-inflammatory effects are represented. These mechanisms include negative interference between PPAR-&gamm; and other nuclear factors such as nuclear factor kappa B (NF-kB), signal transducer and activator of transcription 1 (STAT-1) and activator protein-1 (AP-1). PPAR-&gamm; ligands (L) including dietary fatty acids and endogenous ligands such as arachidonic acid derivatives obtained via the lipoxygenase pathway or via the cyclooxygenase pathway are also shown.
There is growing evidence of the connection between inflammation, tumor development, and NF-κB. Viral oncopogenes, hepatitis B and C proteins, and human papillomavirus infection have been implicated in NF-κB activation. Besides, some chemical and physical carcinogens, especially nicotine and carcinogens in tobacco, can promote cell proliferation, survival and inflammation via NF-κB activation [60]. The role of NF-κB in promoting carcinogenesis is evidenced by numerous studies which indicate that this factor can block apoptosis by regulating anti-apoptotic proteins, including inhibitor of apoptosis proteins (IAPs) or by inhibiting JNK activation and the accumulation of ROS [61]. In chronic inflammation, the cytokines and chemokines produced by inflammatory cells activate NF-κB, which translocates into the nucleus, inducing the expression of certain tumorogenic adhesion proteins, chemokines and inhibitors of apoptosis that promote cell survival. Therefore, NF-κB may contribute to the development of CRC by sustaining the ongoing inflammatory process in the gut mucosa. NF-κB is also connected with the regulation of many genes differently expressed in invasion and metastasis: cyclin D1 and cMyc oncogenes, vascular endothelial growth factor (VEGF), and IL-8 [62]. Several products have been suggested to inhibit NF-κB activation, including curcumin, ginseng extract, resveratrol, green tea extract, among others, being known by their antiproliferative properties [63]. At present, there is significant enthusiasm for the use of specific NF-κB inhibitors as new anti-cancer therapy [64, 65]; however, it is important to introduce some considerations about this kind of new drugs because an ideal inhibitor should prevent NF-κB activation without any apparent effects on other signalling pathways or immunological effects [31].

In colon tumour tissue, expression of PPAR-γ has also been detected in several studies using clinical samples [66]. Activation of PPAR-γ leads to cell differentiation and apoptosis. In addition, PPAR-γ ligands have been shown to be potent inhibitors of angiogenesis, prevention of certain tumorogenic adhesion proteins, chemokines and metastasis, and also to protect against cellular transformation. A recent study on colon induced carcinogenesis by dimethylhydrazine showed a decrease of PPAR-γ expression after tumour induction and that the diclofenac chemopreventive action may be through PPAR-γ activation or overexpression, regulation of COX-2 and the subsequent start of apoptosis [67]. There are very interesting data from the lab of Bassaganya-Riera which have recently observed the beneficial effects of dietary n-3 polyunsaturated fatty acids (PUFAs) in experimental IBD and inflammation-induced CRC through, at least in part, PPAR-γ-dependent mechanism [68]. Further studies are needed to fully elucidate the anti-proliferative and pro-differentiation mechanisms of PPAR-γ activators and their expediency evaluation in the clinical management of CRC.

A leading theory is that the oxidative stress accompanying chronic inflammation contributes to neoplastic transformation. ROS, like the superoxide anion and NO species such as nitric oxide radical (NO•) and its metabolite peroxynitrite, can interact with DNA in proliferating epithelium resulting in permanent genomic alterations. In addition, in colitis-associated colon carcinogenesis, ROS may contribute to the p53 mutations and can functionally impair the protein components of the DNA mismatch repair system [14, 69]. Inducible nitric oxide synthase (iNOS) expression is induced during inflammation and catalyzes the production of NO, however depending on the concentration, genetic background, and type of NOs enzyme, NO may induce protective effects [70]. Clinical data show that iNOS levels are elevated in actively inflamed mucosa from IBD; however, there is controversy about its role in intestinal carcinogenesis [71, 52].

Autophagy plays a dual role in tumorigenesis: the promotion of cell death as a tumor suppressor and the prevention of cell death as an oncogenic mechanism [14]. Mitochondrial DNA is more susceptible to damage due to the lack of repair systems and histone protein protection, and it is thought that autophagy removes damaged mitochondria, thus alleviating oxidative stress to prevent carcinogenesis. However, autophagy is also a cytoprotective mechanism that prevents cells from death under starvation or stress conditions. Studies have shown that ROS can induce autophagy, which instead of causing cell death, protects cells from apoptosis or necrosis, suggesting that autophagy plays both promotion and suppression roles in tumorigenesis [72]. The coordinated regulation of autophagy and apoptosis is essential for cells to make a dynamic choice between death and survival when under stress. These processes are regulated by common factors (p53) although they also share some key autophagy genes (Beclin-1 and Atg5) [73-75]. The tumor-suppressor protein p53 is altered in more than 50% of human cancers and mutation of the p53 gene is one of the most common genetic changes in the development of human colorectal cancer. Recently, this protein has been shown to regulate autophagy [76, 77]: nuclear p53 stimulates autophagy, by this means sustaining the challenge of cells to deal with stress. Meanwhile, cytoplasmic p53 inhibits autophagy by managing the AMP-activated protein kinase (AMPK), a positive regulator of autophagy, and activates mammalian target of rapamycin (mTOR), the main negative regulator [78]. In HCT-116 human CRC cells, loss of p53 impairs autophagic flux upon starvation, culminating in apoptosis [79]. This could explain why some cancer cells retain p53. Although the interplay between autophagy and p53 is complex, the understanding of it would supply new strategies to deal with cancer. Experimental evidence suggests that autophagy is activated by tumor cells as a pro-survival mechanism against cytotoxic agents. Thus, inhibition of autophagy can be used as a tumor cell sensitizing strategy. Along these lines, several CRC cells and others cell lines (HT-29, HTC-116, DLD-1, SW480, WiDr, LoVo, SW620), treated with pharmacological inhibitors of autophagy or subjected to siRNA-mediated downregulation, show increased sensibility to COX inhibition [80], tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-induced cell death [81], aminoacid and glucose deprivation [82], sulfonhane-induced apoptosis [83] and 5-fluorouracil chemotherapy [84].

Sirtuins (SIRT) are a group of highly phylogenetically conserved proteins that occur in organisms from bacteria to human beings, and which catalyzise the deacetylation of target proteins. The deacetylation reaction spends NAD+, a key molecule in energy metabolism, thus linking protein regulatory control to metabolic conditions [85, 86]. SIRT1 deacetylation of p53 causes a weakening of its apoptotic effect. As a consequence, SIRT1 might be considered a facilitator for cancer development. Nevertheless, although pro-oncogenic effects of SIRT1 have been reported in a number of studies, there are also reports showing a tumor suppressor role for this protein [87].

On the other hand, sirtuins have been implicated in circadian rhythms by deacetylating proteins in the clock mechanism of circadian control [88], which establishes a link between sirtuins and metabolism. Interestingly, sleep disruption has been associated with IBD [89] and although information about the role of sirtuins in IBD is limited, there are several reports that show an anti-inflammatory effect for these molecules. Resveratrol, the best known SIRT1 activator, reverses colitis-associated decrease in SIRT-1 gene expression, activation of NF-κB, increase of COX-2 expression, and other changes, in a DSS-induced colitis, and in a spontaneous IL-10− mouse model of colitis [90, 91]. The same authors show that resveratrol suppresses colon cancer associated with colitis [92]. In addition, SIRT1 is a negative regulator of NF-κB activity through the deacetylation of the p65 subunit of NF-κB [93]. Several studies support the notion that SIRT1 could be involved in carcinogenesis [94], and SIRT1 has been found to be up-regulated in various human cancers, including colon cancer [95]. SIRT1 expression is associated with microsatellite instability and CpG island methylator phenotype in human CRC [96]. Conversely, there are also studies showing that SIRT1 can act as tumor suppressor. SIRT1 suppresses intestinal tumorigenesis and colon cancer growth in a β-catenin-driven mouse
model of colon cancer [97]. Abnormal levels of β-catenin may contribute to neoplastic transformation in colon cells [98] and the stability of this protein increases by acetylation [99]. SIRT1 deacetylates β-catenin and promotes cytoplasmic localization of the otherwise oncogenic form of β-catenin [97]. On the other hand, defects in the Wnt signalling, which is upstream of β-catenin, have also been associated to human cancers [100]. SIRT-1 has been shown to regulate Wnt signalling in four colon cancers cell lines (HT-29, HCT-116, RKO and DLD-1) [101]; in this study, SIRT1 promotes constitutive Wnt signaling and Wnt-induced cell migration, therefore presenting more pro-tumor than an anti-tumor effect. In another study, SIRT1 inhibits proliferation of the colon cancer cell line HCT-116 and SIRT1 inhibition promotes colon tumor formation in a tumor xenograft assay [102]. These results show that sirtuins have pleiotropic effects on cancer development demonstrating that there is a wide therapeutic potential for both activators and inhibitors of sirtuins.

Caloric restriction (CR) has long been the only factor able to extend maximum life span in diverse species [103], including primates [104]. Studies on yeast, worms, flies and mice point to a role for nutrient responsive molecules, such as SIRT1 and mTOR, in aging and CR [105]. SIRT1 is proposed to mediate the health benefits of CR showing its capacity to ameliorate degenerative diseases associated with aging [106]. Recently, Firestein et al. [97] have demonstrated that CR induces an increase of SIRT1 expression in the intestine of rodents. Moreover, this study shows that the ectopic SIRT1-induction in a mouse model of colon cancer significantly reduces tumor formation, proliferation and animal morbidity in absence of CR. Autophagy relationship with sirtuins have been demonstrated through AMPK, which senses the intracellular AMP/ATP ratio and inhibits mTOR-dependent signalling [107] while rising cellular NAD+ levels [108]. Consequently, AMPK activation switches on autophagy and increases sirtuin activity. In addition, SIRT1 regulates autophagy by deacetylation of several components of the autophagic cascade [109] and the life-span prolonging effect of sirtuins has been proposed to be mediated by autophagy [110]. Up to date, there are no studies connecting autophagy-sirtuin activity and colon cancer.

The identification of these signals has led to a greater mechanistic understanding of IBD pathogenesis and its evolution to colon cancer, and points to potentially new therapeutic targets.

3. CHEMOPREVENTION AND BIOMARKERS

Chemoprevention is an old concept that consists in the practice of using drugs, vitamins or nutritional supplements to reduce the risk of developing, or having a recurrence of cancer [111, 112]. A number of genetic changes can trigger cells to become cancerous although studying the changes as they occur is difficult, especially in humans. The carcinogenesis is a slow process that could start twenty years before the symptoms appear. That long period of time offers several opportunities for intervention: the original mutation, the transforming and dedifferentiated process or the migration and metastatic movement. Recently, Nature dedicated a supplement to analyze SIRT1 cancer data of interest for cancer prevention; in this publication, Professor Sporn discussed about the state of the art for chemoprevention [113]. The vast majority of cancer research is devoted to find cures, rather than finding new ways to prevent disease. However, common epithelial cancers including lung, colon, pancreas, ovary, skin, prostate and breast, which are responsible for most deaths, have a long latency period of twenty years or more. This latency period is a sufficient occurrence to use preventive drugs that block the development of invasive and/or metastatic disease. With these objectives, cancer chemoprevention uses natural, synthetic or biological substances to reverse, suppress or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer. In this line, induction of apoptosis represents a potent cellular mechanism against cancer. Zhang et al. [114] have recently shown how the selective elimination of premalignant tumour cells by transcription-regulating factors, such as TRAIL and all-trans retinyl acetate (RAC), is an effective method for chemoprevention. In in vivo experimental models of carcinogenesis, it is possible to prevent the onset of cancer in many organs in which carcinoma occurs [113]. Furthermore, chemoprevention has now been clinically validated: selective estrogen receptor modulators (SERMs) can reduce in five-fold the incidence of estrogen receptor-positive breast cancer. In men, antiandrogenic drugs have shown effectiveness in long-term clinical trials for prostate cancer.

Topics to debate include potential toxicity for long term treatments, cost-effective or target population. In such a way, it is suggested stopping doing clinical chemoprevention trials in large populations of people at relatively low risk and focus to the highest risk such as smokers for lung cancer [113]. Individuals identified as being high risk, through use of biomarkers, could receive counseling for life style changes and they might be eligible for chemoprevention [115]. Moreover, using biomarkers to select people for cancer clinical studies would allow for more powerful trials. Anywhere, here the difficulty is finding reliable biomarkers to detect the real process and not false starts; sensitivity and specificity are two essential features and the key to both is finding better biomarkers (genes, proteins and cellular metabolites) that can be measured and associated with the development of cancer. Phosphatidylinositol-3-kinase (PI3K) signalling pathway might be used for chemoprevention and early trials have shown that the administration of a drug that decreases PI3K activity causes regression of abnormal lesions in the airways of high-risk smokers [116]. Other proposals include alteration in gene expression, levels of death-associated-protein kinase or DAR kinase (enzyme implicated in apoptosis), antibodies to mutant p53 (as signal of damage of cell tumour suppressor system), changes in cancer-related genes or markers of inflammation [115].

Many researchers in chemoprevention are beginning to think that perhaps the best way to catch cancer is to target inflammation. Chronic inflammation appears to encourage tumours by prompting the growth of new blood vessels and remodelling extracellular matrix. Thus, it is created a prime setting for normal cell growth to turn malignant [117]. Targeting inflammation might prevent not only cancer but a number of other syndromes or diseases including diabetes, cardiovascular diseases or aging; epidemiological studies with NSAIDs, COX inhibitors (COX-1 or COX-2), may reduce the risk of colon, lung, prostate, brain or skin cancers [118, 119]. Other findings propose that statins, used for cholesterol control, might disrupt the growth and proliferation of cancer cells [120]. Similarly, retrospective studies that may be impractical to confirm prospectively suggest that diabetes treated with metformin have a substantially reduced cancer burden compared with other diabetics. It is unclear if this reflects a chemopreventive effect and thus, developing clinical trials may define important new indications for biguanides in the prevention and/or treatment of many common cancers [121].

4. USE OF DIETARY PHYTONUTRIENTS IN IBD AND COLON CANCER

4.1. Phytonutrients Derived from Fruits and Vegetables

Epidemiological studies have suggested that dietary agents identified from fruits and vegetables contribute to keep balanced cell proliferation and prevent cell carcinogenesis. Furthermore, phytonutrients have received considerable attention because of their low cost and wide safety margin. A substantial amount of evidence from animal and cell culture experiments and some human studies have shown cancer chemopreventive effects from these natural products. However, single-agent intervention has failed to produce the expected outcome in clinical trials; therefore, combinations of them are gaining increasing popularity [122]. A recent study from European Prospective Investigation into Cancer and Nutrition observed
Resveratrol
Genistein
Quercetin

In recent smokers, consumption of vegetables and fruits may reduce lung cancer risk, especially squamous cell carcinomas [123]. However, the chemopreventive properties of plant foods are complicated to demonstrate and several considerations should be taken into account in order to confirm which phytonutrients are cancer preventive agents [124].

Next paragraphs summarize recent advancements on potential colon cancer chemoprevention and mechanistic insight into the actions of the most commonly used and highly researched phytochemicals derived from diet, including curcumin, resveratrol, epigallocatechin gallate (EGCG), quercetin and genistein.

**Curcumin**

Curcumin (diferuloylmethane) (Fig. 3A) is a bioactive substance present in the rhizomes of the herb *Curcuma longa* that has been used for centuries in Asia, both in traditional medicine and in cooking as turmeric which gives food an exotic natural yellow color. This perennial herb has multiple ingredients, including curcuminoids, the most active ingredients for medicinal use [125]. Curcumin has been used for a variety of diseases, including respiratory conditions, inflammation, liver and hepatic disorders, obesity, diabetic wounds, rheumatism and certain tumors [126-130].

At present, no studies in animals or humans have discovered significant toxicity related to curcumin, even at very high doses [131, 132].

**IBD Animal Models and Clinical Studies with Curcumin**

Curcumin has been shown to have preventive as well as therapeutic effects in different experimental models of colitis. Along these lines, treatment with curcumin prior to the induction of colitis mitigated the injurious effects of DSS or trinitrobenzene sulfonic acid (TNBS) via regulation of oxidant/anti-oxidant balance and reduction of serum TNF-α and colonic NO levels [133, 134]. In addition, curcumin blocked NF-κB activation [135, 136] and inhibited TLR-4 expression, which has been shown to induce NF-κB leading to inflammation in the colonic mucosa [137]. Curcumin has also been reported to ameliorate TNBS-induced chronic colitis through decrease of COX-2 expression [138], as well as via suppression of Th1 cytokines expression (IL-12, IFN-γ, TNF-α, IL-1) and increase of Th2 cytokines profile (IL-4 and IL-10) in colon mucosa [139]. Other mechanisms by which the dietary polyphenol curcumin exerts its anti-inflammatory effects in the development of chronic UC include reduction in iNOS expression and activity, inhibition of p38 MAPK signaling [140] and activation of PPAR-γ and its ligands [141]. A recent study has reported the anti-inflammatory effect of the diferuloylmethane administered for two weeks in the spontaneous colitis in IL-10 gene-deficient mice through a reduced production of potent pro-inflammatory mucosal cytokines [142].

Clinical data evaluating the use of curcumin in IBD (including UC and CD) is limited to two studies comprising data for only 99 patients. The first one, conducted by Holt et al. [143] was a small, open-label study, in which curcumin was administered to five patients with UC and five with CD. All proctitis patients improved, with reductions in concomitant medications in four of them and four of five CD patients experienced a reduction in disease activity index scores. Hanai et al. [144] conducted a randomized, multicenter, double-blind, placebo-controlled trial of curcumin plus sulfasalazine or mesalazine compared to placebo plus sulfasalazine or mesalazine in 89 patients with quiescent UC. The relapse rate was significantly higher in the placebo group (20.5%) than in the curcumin-treated group (4.7%). The polyphenol also improved both clinical activity index and endoscopic index scores.

**In vitro Studies with Curcumin in Colon Cancer**

Although the exact mode of action of curcumin is not yet published, pre-clinical studies have shown that curcumin inhibits a number of signaling pathways and molecular targets involved in cancer progression and inflammation [130]. This dietary compound has been reported to exhibit potent *in vitro* antiproliferative and apoptosis-inducing activities in colon cancer cell lines. Along these lines, curcumin treatment induced apoptosis and inhibited colon cancer cell growth via an increase in PPAR-γ, resulting in suppression of cyclin D1 and epidermal growth factor receptor (EGFR) [145] as well as through inhibition of PPAR-8 expression, leading to down-regulation of VEGF [146]. Curcumin has been shown to act synergistically with 5-fluorouracil plus oxaliplatin, a standard chemotherapy for this malignancy, in inhibiting the growth of HCT-116 and HT-29 cells through attenuation of surface growth factor pathways, specifically EGFRs and insulin-like growth factor-1 receptor (IGF-1R), which are considered to play important role in the progression of CRC [147]. Moreover, the diferuloylmethane

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**Fig. (3). Chemical structures of some phytonutrients derived from fruits and vegetables.**

![Image 1](image.png)
induced caspase-3-mediated β-catenin cleavage and c-Myc down-regulation in the Wnt signaling pathway, resulting in G2/M phase arrest as well as increased apoptosis by enhancing the degradation of β-catenin, E-cadherin and APC in HCT-116 cells [148].

Oxidative stress caused by exposure to curcumin has also been implicated in its apoptotic effect [149]. Moreover, Milacic et al. [150] reported that curcumin has proteasome-inhibitory activity, which is a strong apoptotic stimulus for both colon cancer HCT-116 and SW480 cell lines. In addition, Lee et al. [151] demonstrated the apoptotic effects of curcumin on HT-29 colon cancer cells through the AMPK activation and the decrease in pAkt and COX-2 proteins. Other proapoptotic mechanisms of curcumin include induction of p53, overexpression of Bax, down-regulation of Bcl-2 and caspase-3 activation in human colon cancer cells [146, 152].

Biological mechanisms by which curcumin may prevent cancer are also thought to involve the inhibition of NF-κB activation, which may lead to suppression of inducible enzymes expression, such as COX-2, adhesion molecules and inflammatory cytokines [153]. In this line, curcumin inhibited TNF-α-induced COX-2 expression through suppression of NF-κB activity in colon cancer cells. This effect was due to the inhibition of the IκB kinase (IKK) signaling complex that is responsible for the phosphorylation of IκB (IkB) [154]. In a similar report, this substance suppressed cytokine-mediated NF-κB activation with concomitant down-regulation of intercellular adhesion molecule-1 (ICAM-1) and IL-8 gene expression [155]. The pro-inflammatory cytokine IL-8 has been shown to affect cancer progression through angiogenic and mitogenic effects [156]. Curcumin effectively inhibited neurotensin-mediated NF-κB induction and subsequent IL-8 gene induction and migration of HCT-116 colon cancer cells [157].

In addition, curcumin has been reported to inhibit chenodeoxycholate or phorbol ester-mediated induction of COX-2 and the subsequent synthesis of prostaglandin E2 in a number of gastrointestinal cell lines [158]. Goel et al. [159] showed that curcumin specifically inhibited COX-2 but not COX-1 expression in HT-29 human colon cancer cells. Cotreatment with curcumin and celexob, a selective COX-2 inhibitor, synergistically inhibited colon cancer cell growth and induced apoptosis through mechanisms involving down-regulation of COX-2 expression [160]. Du et al. [161] reported similar results after combination of curcumin and 5-fluorouracil. The overexpression of metalloproteinases (MMPs) has been reported in colorectal cancer and plays an important role in neoplastic cell proliferation and metastasis. Curcumin suppressed cell migration of the human colon cancer cell line, Colo 205, by downregulating COX-2 and matrix metalloproteinase-2 expressions [162]. Curcumin has been shown to inhibit vascular tube formation, which may explain its chemopreventive effect at the level of tumor growth and metastasis. These antiangiogenic properties have been shown to be mediated in part by down regulation of COX-2 expression and prostaglandin E2 (PGE2) production in human intestinal microvascular endothelial cells [163].

**Animal Studies with Curcumin in Colon Cancer**

Curcumin has also shown promise as a chemopreventive agent because of its in vivo regression of various animal models of colorectal carcinogenesis. Along these lines, curcumin treatment to mice bearing xenografts of colon cancer HCT-116 cells resulted in tumor growth inhibition, associated with proteasomal inhibition, growth arrest and stimulation of apoptosis [150]. Li et al. [164] demonstrated that liposomal curcumin inhibited colon carcinoma growth in Colo205 and LoVo xenografts and these effects were accompanied by a potent antiangiogenic response, as shown by reduction in CD31 (an endothelial marker), VEGF and IL-8 expression. Another interesting study reported that cotreatment of curcumin and resveratrol was more effective than either agent alone in inhibiting growth of p53-positive (wt) and p53-negative colon cancer HCT-116 cells in vitro and in vivo in SCID xenografts of colon cancer HCT-116 (wt) cells [165].

Since adenomas are generally regarded as precursor lesions of colorectal cancer, several reports have examined the effect of dietary curcumin in the adenomatous polyposis coli (ApcMin+) mouse, a model of human familial adenomatous polyposis. These animals are genetically predisposed to develop intestinal tumors as a result of a mutation of the Apc gene [166]. The results of these studies have shown that curcumin retarded adenoma growth, reflected by total number of adenomas and mean adenoma size [167, 168]. This effect may be mediated by the inhibition of COX-2 protein expression and the reduction of levels of two oxidative DNA adducts in intestinal adenoma tissue [169]. Curcumin also decreased expression of the oncprotein β-catenin in the enterocytes of the ApcMin+ mouse [167]. Another paper examining the effects of curcumin on intestinal inflammation in this mouse model, has reported that this compound decreased total intestinal polyps by 75% as well as mRNA and protein expression of IL-1β and chemokine ligand 2 (CCL2), suggesting that the benefits of curcumin in colon cancer may be, at least in part, mediated by its antiinflammatory activity [170].

The colon carcinogens 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM) produce their effects through a series of early steps involving inflammation, increased cell proliferation in colon crypts, epigenetic and genetic alterations and late events such as decreased sensitivity to apoptosis induction resulting in the development of cancer [171]. Curcumin administration during initiation, postinitiation and promotion/progression phases of AOM-induced colon carcinogenesis in rats significantly inhibited tumor development in a dose-dependent manner and increased apoptosis in the colonic tumors [172, 173]. It has also been shown that combination of curcumin and celecoxib suppressed DMH-induced colon carcinogenesis in rats by decreasing the average number of aberrant crypt foci (ACF) [174]. Similarly, cotreatment of dietary curcumin and green tea catechins had a preventive effect in this model of carcinogenesis since this combination inhibited the total number of ACF and the proliferation index as well as increased the apoptotic index [175].

It has been shown that cyclic administration of DSS in drinking water results in the establishment of chronic colitis and the development of colorectal dysplasias and cancers with pathological features that resemble those of human colitis-associated neoplasia [51]. Villegas et al. [176] have recently demonstrated the protective effect of dietary curcumin in this model of chronic colitis-associated CRC through a reduction in β-catenin expression and in the production of the proinflammatory cytokines TNF-α and IFN-γ.

**Clinical Studies with Curcumin in Colon Cancer**

Curcumin has been evaluated as a potential chemopreventive and/or chemotherapeutic agent in several different clinical trials [177, 178]. In a phase I clinical trial, fifteen patients with advanced CRC refractory to standard chemotherapies received curcumin daily between 0.45 and 3.6 g daily for up to 4 months. Consumption of 3.6 g of curcumin daily generated detectable levels of curcumin and its glucuronide and sulfate metabolites in plasma and urine as well as caused inhibition of PGE2 production in blood leukocytes measured ex vivo [179]. More recently, Carroll et al. [180] evaluated the effects of oral curcumin (2 g or 4 g per day for 30 days), in a nonrandomized and open-label clinical trial, in 44 eligible smokers with eight or more ACF on screening colonoscopy. The results showed a significant 40% reduction in ACF number occurred with the 4-g dose, whereas ACF were not reduced in the 2-g group. Another study showed that curcumin treatment improved the general health of patients with CRC by decreasing serum TNF-α levels and increasing apoptotic tumor cells and expression of p53 in tumor tissue [181]. The combination of curcumin and quercetin reduced the number and size of ileal and rectal adenomas in five
patients with familial adenomatous polyposis without appreciable toxicity, after six months of treatment [182].

**Resveratrol**

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) (Fig. 3B) is a polyphenolic phytoalexin synthesized by plants in response to stress and invasion of other pathogens. It is found in grape skins, red wine, peanuts, mulberries and cranberries. Resveratrol is formed by a condensation reaction between 3 molecules of malonyl CoA and a molecule of 4-coumaroyl coacatalyzed by resveratrol synthase [183]. Both the cis and trans forms coexist; however, trans is the biologically active form [184]. Numerous in vitro and animal studies show that resveratrol has potent antioxidant, anti-aging, anti-inflammatory and anti-cancer effects, promotes vascular endothelial function and enhances lipid metabolism [185-187].

**IBD Animal Models with Resveratrol**

Resveratrol has been evaluated for its beneficial effects in several UC models. This natural compound ameliorated DSS-induced acute inflammation in mouse colonic mucosa through inhibition of iNOS expression and NF-κB, signal transducer and activator of transcription-3 (STAT3) and extracellular signal-regulated kinase (ERK) activity [188]. The inhibitory effects of resveratrol in this model of UC were also associated with its antioxidative effect and the reduction in the expression levels of TNF-α, IL-8 and IFN-γ [189]. In addition, this polyphenol decreased COX-2 expression and PGD2 concentration and enhanced apoptosis in rats with TNBS-induced acute colitis [190]. Resveratrol has also been reported to abrogate chronic colitis by inducing SIRT1 expression with consequent decrease in NF-kB activity [90]. Other mechanisms involved in the beneficial effects of resveratrol in DSS-induced colitis model include inhibition of pro-inflammatory factors, such as TNF-α, IL-1β and NO levels and prostaglandin E synthase-1 (PGES-1), COX-2 and iNOS expression, as well as increase of the anti-inflammatory cytokine IL-10 [191, 192]. In addition, oral administration of resveratrol ameliorated the established chronic colitis in IL-10 (-/-) mice by inducing immunosuppressive CD11b(+) Gr-1(+) cells in the colon. This study also reported that resveratrol decreased local and systemic inflammatory cytokine concentrations, including IFN-γ, TNF-α, IL-6, RANTES, IL-12 and IL-1β [193].

**In vitro Studies with Resveratrol in Colon Cancer**

A significant number of in vitro studies have shown that induction of apoptotic cell death and inhibition of cell cycle progression are the two major pathways responsible for the chemopreventive role of resveratrol in colon cancer. This compound has been shown to elicit apoptotic signaling via mitochonfdria. Mohan et al. [194] reported that caspase-2 activation occurred upstream of mitochondria in the colon cancer cells HCT-116 treated with resveratrol. The activated caspase-2 triggered mitochondrial apoptotic events by inducing conformational changes in Bax/Bak with subsequent release of cytochrome c, apoptosis-inducing factor and endonuclease G. Lee et al. [195] identified caspase-6 activation and lamin-A cleavage as a major signaling pathway in resveratrol-evoked apoptosis in HCT-116 human colon carcinoma cells. The antiapoptotic effects of resveratrol were significantly mitigated in the absence of the tumor suppressor protein p53. These authors also reported that the polyphenol, at high concentrations, synergistically promoted 5-Fluorouracil-mediated colon cancer cell apoptosis through enhancement of caspase-6 activity irrespective of p53 status. Conversely, lower doses of resveratrol displayed antagonistic effects on cell apoptosis [196]. In another study, resveratrol induced apoptosis in the colon carcinoma cell line HCT-116 regardless of p53 status and at concentrations comparable to those found in wine and grapes [197]. Park et al. [198] demonstrated that resveratrol-induced apoptotic cell death in HT-29 cells was associated with its ability to induce ER stress response.

Insulin-like growth factor-1 receptor (IGF-1R) is overexpressed during colon carcinogenesis. Upon IGF-1 binding, IGF-1R activates the PI3K/Akt cascade [199], which stimulates the Wnt/β-catenin pathway, among others [200]. This signaling pathway plays a central role in elevating colonocyte proliferation and suppressing apoptosis in colon cancer [201]. Resveratrol has been shown to suppress colon cancer cell proliferation and elevate apoptosis after IGF-1 exposure through suppression of IGF-1R/Akt/Wnt signaling pathways as well as activation of p53 [202]. Moreover, this polyphenol significantly decreased the amount and proportion of β-catenin in the nucleus of colon cancer cell line RKO [203].

It was reported the involvement of mitochondrial ROS on anti-tumoral activity of this bioactive compound in the human colorectal carcinoma cell line HT-29 [204]. Resveratrol has also demonstrated anti-inflammatory effects, through inhibition of NOS enzyme activity [205] and increase of PPAR-γ activity in Caco-2 cells [206]. In addition, Zykova et al. [207] showed that the anticancer effects of resveratrol were mediated directly through COX-2 and that this polyphenol decreased COX-2-mediated PGE2 production in HT-29 cells.

Resveratrol has also been shown to exhibit antimitastatic effects through its potent inhibition of cell adhesion, migration and invasion, as well as reduction of secretion of MMP-9 and MMP-2 in Lovo cells cultured under normoxia and hypoxia [208]. Kimura et al. [209] reported that antimitastatic actions of resveratrol were probably due to the inhibition of VEGF-induced angiogenesis.

**Animal Studies with Resveratrol in Colon Cancer**

Schneider et al. [210] showed that orally administered resveratrol decreased the number of tumors in the small intestine and prevented tumor formation in the colon of Apcmin/+ mice. Moreover, these authors demonstrated that resveratrol downregulated genes known to be implicated in cell cycle progression, such as cyclins D1 and D2, as well as upregulated a panel of genes controlling the activation of immune response and the inhibition of the carcinogenic process and tumor expansion.

Chronic resveratrol supplementation has been shown to suppress DMH-induced colon carcinogenesis at various stages through reduction of the ACF incidence, tumor development, free radical-mediated oxidative stress, cell proliferation and cancer-associated bacterial enzyme activities, when supplemented throughout the experimental period [211, 212]. Moreover, these authors reported that mechanisms underlying the potential chemopreventive effect of resveratrol in this model of colon carcinogenesis included down-regulation of the expression of inflammatory, cell proliferative and apoptotic biomarkers such as COX-2, ornithine decarboxylase, caspase-3 and heat shock proteins 70 and 27 [213].

Studies on the effects of resveratrol on AOM-induced carcinogenesis revealed a significant reduction in the number and multiplicity of ACF in the colorectal mucosa by modulation of Bax and p21 expression [214]. Similarly, a recent paper has reported that this polyphenol prevented the onset of colon cancer in a mouse model of colitis-driven colon cancer [91]. It has also been reported the inhibitory effect of dietary administration of pterostilbene, a natural dimethylated analogue of resveratrol, against the formation of AOM-induced ACF and adenomas, by suppressing the proliferation of malignant colonocytes and abnormal expression of NOS and COX-2 as well as inducing apoptosis in the colonic crypts [215, 216]. In addition, this compound downregulated the expression of β-catenin and cyclin D1, and reduced the levels of TNF-α, IL-1 β and IL-4 and nuclear staining for phospho-p65, a key molecule in the NF-kB pathway [217].

**Clinical Studies with Resveratrol in Colon Cancer**

Nguyen et al. [218] conducted a phase I pilot clinical trial in patients with colon cancer to evaluate the effects of a low dose of plant-derived resveratrol and resveratrol containing freeze-dried
grape powder (GP) on Wnt signaling in the colon. The results showed that resveratrol in combination with other bioactive compounds in GP inhibited Wnt pathway in normal colonic mucosa, as indicated by a reduction in the expression of a panel of Wnt target genes. In another recent study, twenty patients with confirmed colorectal cancer, who were to undergo surgical resection of their malignancy, received eight daily doses of resveratrol at 0.5 or 1.0 g before surgery. Consumption of resveratrol significantly reduced colon tumor cell proliferation, as reflected by reduction in Ki-67 staining, a surrogate marker of cell growth [219]. Further clinical studies of dietary supplementation with resveratrol as a potential colon cancer preventive strategy are needed.

Epigallocatechin Gallate

Green tea (Camellia sinensis) contains several polyphenolic compounds, including the catechins (-)-epigallocatechin gallate (EGCG) (Fig. 3C), (-)-epigallocatechin (EGC), epicatechin-3-gallate (ECG) and (-)-epicatechin (EC) [220]. Among the green tea constituents, EGCG is the major biologically active compound, which has been shown to possess in vitro and in vivo anti-inflammatory and anti-oxidant properties, responsible for their cancer chemopreventive potency [221, 222].

IBD Animal Studies with EGCG

Recent studies show the beneficial effects of EGCG in different experimental models of colitis. These effects were associated with a significant reduction of NF-κB and (AP-1) activation [223], as well as an inhibition of TNF-α and IFN-γ production. EGCG also showed antioxidant activity via decreasing NO and malondialdehyde (MDA) and increasing superoxide dismutase (SOD) in colonic mucosa [224]. Furthermore, EGCG ameliorated acute experimental IBD and the induction of pro-inflammatory cytokines, including IL-1α, IL-6, IL-12 and IL-18 [235]. EGCG has been also reported to prevent the formation of colon ACF induced by 2-amino-3-methylimidazo[4,5-f] quinoline in mice [236] and rats [237]. Another study examined the effects of EGCG on the development of AOM-induced colonic premalignant lesions in C57BL/6j-db/db mice, which are obese and develop diabetes mellitus. EGCG administration in drinking water effectively suppressed the development of aberrant crypt foci, thus suggesting the inhibitory effects of EGCG on the early phase of obesity-related mouse colon carcinogenesis. In addition, this suppressing effect of EGCG was associated with the improvement of hyperlipidemia and hyperinsulinemia and a depressant effect on the IGF/IGF-IR axis [238], which is involved in the development, progression and metastatic potential of CRC [239]. Furthermore, Ju et al. [240] reported that EGCG effectively inhibited intestinal tumorigenesis in Apcmin−/− mice, possibly through the attenuation of the carcinogenic events, which include aberrant nuclear β-catenin and activated Akt and ERK signaling.

Clinical Studies with EGCG in Colon Cancer

Hoensch et al. [241] conducted a controlled, prospective and observational pilot study where long-term treatment with a tea-based flavonoid mixture (daily standard dose 20 mg apigenin and 20 mg EGCG) reduced the recurrence rate of colon neoplasia in high risk patients particularly in those with resected colorectal cancer. Since data evaluating the efficacy of this phytochemical in cancer chemoprevention are limited, future clinical studies are needed.

Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) (Fig. 3D) is a typical flavonoid, the most well defined group of polyphenolic compounds and is abundant in many commonly consumed fruits and vegetables, including apples, cranberries, blueberries, leek and onions [242, 243]. It has been reported that the average intake of flavonoids is 23 mg per day with quercetin contributing with almost 70% [244, 245]. Flavonoids in general are considered as non-absorbable due to being bound to sugars as beta-glycosides. Hydrolysis causing their absorption can only occur in the colon by microorganisms [244]. Quercetin is usually present in glycosylated forms, such as quercitrin (3-rhamnosylquercetin) and rutin (3-rhamnosyl-glucosylquercetin). Quercetin and its glycosides have been reported to display a number of biochemical and pharmacological activities, including anti-viral, anti-microbial, anti-allergic, anti-inflammatory and anti-cancer effects [246, 247].

IBD Animal Studies with Quercetin

Previous papers have shown that quercetin and rutin exert intestinal anti-inflammatory effects in experimental models of rat colitis, whereas no clear effects have been demonstrated for the aglycone form quercetin. The beneficial effects of quercitrin were associated with a reduction in colonic MDA levels and alkaline phosphatase activity as well as with an improvement in the colonic oxidative status [248, 249]. Moreover, an inhibition of NOS activity, probably related to a decreased expression in the inducible form of the enzyme via downregulation of NF-κB activity was also reported after chronic treatment with quercitrin [250, 251]. Kwon et al. [252] demonstrated that a diet containing rutin, but not quercetin, ameliorated DDS-induced colitis, presumably by suppressing the induction of pro-inflammatory cytokines, including IL-1β and IL-6. These authors suggested that rutin may be useful for the prevention and treatment of IBD and colorectal carcinogenesis via attenuation of pro-inflammatory cytokine production.
**In vitro Studies with Quercetin in Colon Cancer**

The effects of quercetin on colon cancer have been largely analyzed in cell culture models. This flavonoid inhibited cell growth and induced apoptosis in a number of colon cancer cells, including HT-29, Caco-2, SW480 and 786 [255-258]. Kim et al. [259] reported that these antitumor effects may be mediated, in part, by the ability of quercetin to downregulate ErbB2/ErbB3 signaling and the Akt pathway, which have been associated with the development of human colon cancer. In addition, quercetin suppressed cell growth, arrested the cell cycle at the sub-G1 phase and induced apoptotic death in both breast and colon cancer cells through the activation of AMPK signaling. This activation seemed to be closely related to a decrease in COX-2 expression [257, 258]. It has been reported that some chemopreventive agents, including quercetin, kaempferol, genistein, resveratrol and resorcinol suppressed both transforming growth factor (TGF)-α-stimulated and non-stimulated COX-2 promoter activities in human colon cancer DLD-1 cells [259]. Furthermore, the antitumor effects of quercetin have been related to the inhibition of cyclin D1 and survivin expression as well as the downregulation of transcriptional activity of β-catenin/Tcf in SW480 colon cancer cells transiently transfected with the TCF-4 reporter gene. This signaling pathway has been shown to play a pivotal role in cellular developmental processes and human carcinogenesis [260].

This flavonoid has also shown to have cancer-preventive effects through its strong antioxidative properties [261]. In this respect, the cytoprotective ability of certain dietary flavonoids, including quercetin, against oxidative DNA damage induced by hydrogen peroxide in Caco-2 cells was reported [262]. In human lymphocytes the flavonoids quercetin and rutin showed a dose-dependently protective effect against DNA damage caused by the mutagenic anticancer drug mitomycin C [263]. In the same line, a significant protective effect of these two flavonoids has been recently demonstrated after DNA damage had been induced in vitro by two food mutagens in lymphocytes obtained from colon cancer patients, which had increased basal DNA damage possibly due to an overproduction of ROS [264]. Thus, dietary supplementation with flavonoid-rich vegetables and fruits may prove very effective in protecting against oxidative stress.

**Animal Studies with Quercetin in Colon Cancer**

The liposomal quercetin significantly inhibited solid tumors growth in different murine models, including BALB/c mice bearing CT26 colon adenocarcinoma. The mechanisms underlying this antitumor effect were related with inhibition of tumor angiogenesis, induction of apoptosis and downregulation of heat shock protein 70 expression in tumor tissues [265]. Dietary quercetin has also been described to reduce AOM-induced colorectal carcinogenesis in rats [266-269]. The flavonoids quercetin, curcumin, rutin and silymarin evoked apoptosis in the large intestine, with quercetin being the most potent [270]. Choi et al. [271] evaluated the effect of quercetin intake in the AOM model as well as inflammatory response in rats fed with high-fat diet rich in omega-6 fatty acids. These authors reported that quercetin supplementation reduced the number of ACF in animals fed high-fat diet, however, no significant changes in COX-2 and iNOS expression were found after quercetin administration. In a similar study, this flavonoid inhibited the formation of early preneoplastic lesions in the AOM model, which was associated with reductions in proliferation and increases in apoptosis. The protection conferred by quercetin may be in part due to a suppression of proinflammatory mediators expression typically upregulated at disease onset, such as COX-2 [272]. A recent study has reported that quercetin decreased polypl number and size in the ApcMin mouse model of intestinal tumorigenesis and that these effects may be related to a reduction in macrophage infiltration [273].

**Clinical Studies with Quercetin in Colon Cancer**

Bobe et al. [274] have recently conducted a 4-year randomized, multi-center, nutritional intervention trial to evaluate the effect of intake of flavonols, especially isorhamnetin, kaempferol and quercetin, in 872 patients presenting at least one histologically confirmed colorectal adenoma. This study reported a reduction in serum IL-6 concentrations, associated with a decreased risk of adenoma recurrence and higher flavonol intake.

**Genistein**

Asian diet contains high amounts of soy and soy products, which are rich in isoflavones, plant-derived polyphenols. Soy intake has long been recognized to reduce the incidence of different cancers, cardiovascular disease, postmenopausal syndrome, diabetes mellitus and osteoporosis [275-277]. One of the most abundant and the best-characterized dietary isoflavones is genistein (4,5,7-trihydroxyisoflavone) (Fig. 3E). Like other isoflavones, genistein is capable of binding to the estrogen receptor, with a preference for receptor β, the predominantly expressed receptor subtype in the gastrointestinal tract and to trigger mechanisms of estrogen action [278]. Genistein reproduced the health benefits of soy, lowering the incidence of cardiovascular diseases [279], preventing osteoporosis and attenuating postmenopausal problems [280]. Furthermore, it has been reported that genistein exerts important metabolic and hormonal changes, including decrease of body mass and fat tissue, accompanied by a decreased appetite and alteration of expression of genes engaged in lipid metabolism and glucose transport into cells affecting lipolysis, lipogenesis and ATP synthesis [281].

**IBD Animal Studies with Genistein**

Genistein has shown beneficial anti-inflammatory effects in a rodent model of TNBS-induced chronic colitis through reduction in mieloperoxidase (MPO) activity and COX-2 mRNA and protein expression [282].

**In vitro Studies with Genistein in Colon Cancer**

Several in vitro studies have demonstrated that genistein has anti-cancer effects in prostate, breast, colon, gastric, lung and pancreatic adenocarcinomas and in lymphoma [276]. Genistein has been reported to inhibit cell growth and induce apoptosis in a number of colon cancer cell lines [283, 284]. The mechanisms involved in genistein’s anti-cancer properties include inhibition of IGF-IR signaling and attenuation of the PI3K/Akt pathway activity, which is known to be critical in the regulation of colon cancer progression [285]. Additionally, the inhibitory effect of genistein in mouse colon cancer MC-26 cells involved activation of transforming growth factor-beta1 (TGF-B1)/Smad signaling [286], which has been shown to be associated with cell proliferation inhibition and induction of growth arrest and apoptosis in epithelial tissue [287]. Genistein has also been reported to induce apoptosis through the overexpression of Bax and the down-regulation of Bcl-2 in human colon cancer HT-29 [288]. The protective effect of genistein has been also attributed, in large part, to their antioxidant properties. Besides scavenging free radicals, this isoflavone stimulated antioxidant protein gene expression, such as metallothionein and catalase in Caco-2 cells [289].

Genistein has been shown to suppress metastasis in different cancer types, including colon cancer. Genistein reduced experimental lung metastasis of murine colon 26-L5 carcinoma cells by 44% [290]. It has been reported that epigenetic modifications, such as DNA promoter methylation and histone modification, play crucial roles in regulating the expression of many metastasis suppressor genes, which indicates the association between aberrant epigenetic alterations and cancer metastasis [291]. Genistein has been shown to regulate epigenetic alterations of various genes in cancer cell lines [292, 293]. It has been proposed that those changes may contribute to the function of this isoflavone in the inhibition of CRC metastasis [291]. Genistein has been reported to regulate specific
genes in the Wnt signaling pathway in colon cancer cells, by inducing Wnt5a expression, which was accompanied by a decrease in DNA methylation level at the analyzed CpG island [294].

A recent study has demonstrated that a mixture of soy isoflavones (genistein, daidzein and glycitein) inhibited proliferation and growth of DLD-1 human colon adenocarcinoma cells by causing arrests at G2/M phase of the cell cycle. Moreover, these authors showed that estrogen receptor-β is involved in the growth-suppressive effects of soy isoflavones [295]. Since the loss of the expression of this receptor is a common step in estrogen-dependent tumor progression in colon [296], upregulation and activation of receptor estrogen-β status by specific food-borne-ligands such as soy isoflavones could potentially be a dietary prevention or therapeutic strategy for colon cancer.

Furthermore, combination of 5-fluorouracil and genistein inhibited cell growth, induced apoptosis and ROS generation as well as inhibited COX-2 expression and PGE2 production in colon cancer cells through phosphorylation of AMPK [297]. Co-treatment with indole-3-carbinol, derived from Cruciferous vegetables and genistein synergistically induced apoptosis in human colon cancer HT-29 cells by simultaneously inhibiting the phosphorylation of Akt and progression of the autophagic process [298]. Another study reported that genistein increased the cytotoxic levels and growth inhibitory activities of EGCG against human colon cancer cells.

**Animal Studies with Genistein in Colon Cancer**

The potential of soy isoflavones to reduce colon cancer has also been investigated in animal experiments. These studies have found controversial results depending on soy isoflavones dose and the animal model. In this line, a recent study showed that a diet containing different isoflavones (genistein, daidzein and equol) reduced ACF formation and COX-2 expression in a dose-independent manner in model of colon carcinogenesis induced by DMH [299]. However, other studies reported that genistein or soy isoflavones did not protect animals from colon tumor development [300, 301]. Moreover, the combination of 0.01% EGCG in the drinking fluid and 0.2% genistein in the diet enhanced intestinal tumorigenesis in male ApcMin+ mice [302].

**Clinical Studies with Genistein in Colon Cancer**

Data from epidemiologic studies evaluating the preventive effects of soy or isoflavones on colon cancer are inconsistent [303]. Adams et al. [304] found no reduction in colorectal epithelial cell proliferation after a 12-month dietary soy isoflavone intervention in a randomized controlled trial conducted in men and women with previous adenomatous polyps. In relation to colonic adenoma development two studies have examined the effect of soybean food consumption on polyp growth [305, 306]. Although the findings from both studies suggest an inverse relationship between the intake of miso soup [305] or tofu [306] and the development of colorectal adenomas, this relationship was not found to be significant.

4.2. Marine Natural Products: Microalgae as a Source of Bio-molecules with Potential in IBD and Cancer

Traditionally, earth’s natural products have been studied to a great extent and have been used therapeutically. Early research focused on inland compounds, but in the last 30 years the need of new therapeutic molecules has given rise to a vast number of studies in marine invertebrates and microalgae. We have witnessed the discovery of many new interesting compounds, which are commonly referred to as marine natural products. The large diversity found in the marine environment allows for the recollection of multiple molecules as well as it represents a huge source to isolate new microbes such as bacteria, cyanobacteria, fungi, algae or small invertebrates such as sponges, tunicates, bryozoans and mollusc [307]. It has been demonstrated that many of these molecular structures may be potentially useful to be used as drugs in the treatment of diseases such as cancer, chronic inflammation, infections or neurological disorders. Therefore, these organisms constitute extremely important oceanic resources, covering more than 90% of the oceanic biomass [308]; they are taxonomically diverse, largely productive and biologically active.

Biotechnology of microalgae was first developed during the 1960’s and now is a major field of study for both research and industry. Currently, about 30,000 species of microalgae are known and only twelve are cultivated on an industrial scale, thus constituting a natural source of secondary metabolites. Being photautrophics, their simple growth requirements, in contrast to macroalgae, make them attractive for demand by the pharmaceutical, food, cosmetic and biodiesel industry. Algae, including both prokaryotic and eukaryotic organisms, can perform photosynthesis more efficiently than the plants themselves. They have a great capacity to adapt to different environmental conditions that make them suitable for living in different types of terrestrial or aquatic environment. In addition to their varying evolutionary histories or environmental features specific to the oceans, these organisms adapt their metabolism to different environmental conditions, producing marine natural products which possess different structural characteristics regarding to their terrestrial counterparts. The marine life forms have evolved into different secondary metabolites to some extent, besides hand their natural products are also unique in their frequent incorporation of halogen atoms from the surrounding sea water [309].

Nowadays, microalgae are considered rich sources of bioactive molecules, including carotenoids, polysaccharides and long-chain polyunsaturated fatty acids. These compounds have been shown to possess promising pharmaceutical potential because of their anti-inflammatory, antimicrobial, antiviral and antitumoral activities [310, 311]. Along these lines, β-carotene, a known antioxidant whose main sources are Dunaliella and Haematococcus, has been used as chemopreventive agent and for the treatment of neurogenerative diseases. Other interesting molecules synthesized by microalgae with pharmacological applications include fatty acids, used as anti-inflammatory agents or for cardiovascular diseases (Chlorella); phycobiliproteins used as immunomodulatory, antioxidant or anticancer factors (Spirulina); sulfated polysaccharides used as anti-viral (Porphyridium); vitamins, phenolic or volatile compounds, used as anti-microbial and antioxidants (Spirulina) (see Table 1). The most studied bioactive compounds synthesized by microalgae are described below.

**Carotenoids**

Carotenoids have received increasing attention because of the decreased incidence of cancers associated with their consumption. The main carotenoids are carotenes and xanthophylls. They are lipid components which can be found in plants and algae as well as in non-photosynthetic organisms such as animals, fungi and bacteria. They are recognized by the red, orange or yellow appearing on the leaves, flowers or fruits, the color of bird feathers, shells of crustaceans and the scales and skin of fish [312]. It has been shown the antioxidant activity of many pigments including carotenoids that confers a protective role against oxidative stress in multiple contexts. In the human case, this protection is presumably the cause of improved health associated with consumption of these compounds. On the other hand, these products are widely used as colorants in the food industry and in aquaculture as essential components for proper growth and reproduction of species with commercial value. Marine microalgae contain up to 0.2% of carotenoids (w/w dry weight) and may thus be of high interest as functional food to prevent cancer. For this reason, microalgae are currently being studied as chemopreventive agents in numerous in vitro and in vivo inflammation models [313-315].

Microalgae as Dunaliella, Haematococcus or Chlorella are an important source of carotenoids [316] and for this reason, they are currently being studied for their potent antioxidant activity (food...
### Table 1. Potential Functional Ingredients found in Microalgae, Biologic Activity and Examples of these Bioactivities

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Biologic Activity</th>
<th>Microalgae</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carotenoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-carotene</td>
<td>Antioxidant activity</td>
<td><em>Dunaliella salina</em></td>
<td>[405]</td>
</tr>
<tr>
<td></td>
<td>Anticancer (lunch, mouth, stomach, breast)</td>
<td><em>Haematococcus pluvialis</em></td>
<td>[406]</td>
</tr>
<tr>
<td>Astaxanthin</td>
<td>Antioxidant and anti-inflammatory activity and cancer prevention</td>
<td><em>Haematococcus pluvialis</em></td>
<td>[406]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Chlorella vulgaris</em></td>
<td>[407]</td>
</tr>
<tr>
<td>Lutein</td>
<td>Antioxidant activity</td>
<td><em>Chlorella pyrenoidosa</em></td>
<td>[408]</td>
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<tr>
<td></td>
<td></td>
<td><em>Haematococcus pluvialis</em></td>
<td></td>
</tr>
<tr>
<td>Violaxanthin</td>
<td>Antioxidant activity</td>
<td><em>Chlorella ellipsoidea</em></td>
<td>[326]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Dunaliella tertiolecta</em></td>
<td>[313]</td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>Antioxidant activity</td>
<td><em>Picochlorum sp</em></td>
<td>[409]</td>
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<td></td>
<td></td>
<td><em>Nannochloris</em></td>
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<td></td>
<td></td>
<td><em>Haematococcus pluvialis</em></td>
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<tr>
<td><strong>Fatty acids</strong></td>
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<tr>
<td>Oleic acid</td>
<td>Antioxidant activity</td>
<td><em>Haematococcus pluvialis</em></td>
<td>[410]</td>
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<tr>
<td></td>
<td></td>
<td><em>Chlorella vulgaris</em></td>
<td>[411]</td>
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<tr>
<td></td>
<td></td>
<td><em>Dunaliella salina</em></td>
<td>[412]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Spirulina platensis</em></td>
<td>[413]</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Antioxidant and antimicrobial activity</td>
<td><em>Dunaliella salina</em></td>
<td>[412]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Spirulina platensis</em></td>
<td>[414]</td>
</tr>
<tr>
<td>Docosahexanoic acid (DHA)</td>
<td>Anti-inflammatory, reduce risk of certain heart diseases and anti-proliferative</td>
<td><em>Spirulina platensis</em></td>
<td>[415]</td>
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<tr>
<td></td>
<td></td>
<td><em>Nannochloropsis oculata</em></td>
<td>[416]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Cryptothecodinium cohnii, Schizochytrium sp.</em></td>
<td>[37]</td>
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<tr>
<td></td>
<td></td>
<td><em>Nitzschia laevis</em></td>
<td></td>
</tr>
<tr>
<td>Eicosapentaenoic acid (EPA)</td>
<td>Anti-inflammatory, reduce risk of certain heart diseases and anti-proliferative</td>
<td><em>Nannochloropsis oculata</em></td>
<td>[416]</td>
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<tr>
<td></td>
<td></td>
<td><em>Spirulina platensis</em></td>
<td>[417]</td>
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<td></td>
<td></td>
<td><em>Porphyridium cruentum</em></td>
<td>[378]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Cryptothecodinium cohnii, Schizochytrium sp.</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Nitzschia laevis</em></td>
<td></td>
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<tr>
<td><strong>Proteins</strong></td>
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<tr>
<td>Phycobiliproteins (phycocyanin and allophycocianin)</td>
<td>Antioxidant activity</td>
<td><em>Spirulina plantensis</em></td>
<td>[418]</td>
</tr>
<tr>
<td><strong>Polysacharides</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Sulfated polysaccharide</td>
<td>Antiviral, anticancer, anti-hyperlipidemia, and anticoagulant</td>
<td><em>Porphyridium</em></td>
<td>[361]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Chlorella autotrophica</em></td>
<td>[362]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Isochrysis sp</em></td>
<td></td>
</tr>
<tr>
<td>Insoluble fiber</td>
<td>Reduce total and LDL cholesterol</td>
<td><em>Chlorella vulgaris</em></td>
<td>[419]</td>
</tr>
</tbody>
</table>
Xanthophylls are yellow or brown pigments belonging to the carotenoids group, and they were first isolated from crab *Astacus astacus*. They are also found in plants, yeast, trout, salmon and shellfish, feathers of some birds and specially, in microalgae.

Different xanthophylls have been described, including flavoxanthin, lutein, cryptoxanthin, rubixanthin, violaxanthin, rodoxanthin, cantaxanthin, zeaxanthin and astaxanthin, all of them known for their antioxidant activity. Among them, the most studied are astaxanthin, lutein, violaxanthin and zeaxanthin. Their antioxidant properties are related with their anti-free radical activities. Free radicals and ROS are constantly produced by cells as part of their metabolic processes [327]. Humans have well-developed defence systems that generally maintain an equilibrium between free radicals and antioxidants [328]. However, under conditions of elevated oxidative stress, for example, aging [329] and chronic diseases [330] or the phagocytes when generates an excess of free radicals to aid in their offensive degradation of the invader, defences may be overwhelmed [331], causing an imbalance in cellular processes that results in the attack of cellular components. Oxidative stress can lead to the oxidative damage of DNA, producing significant base damage, strand breaks, altered gene expression, and, ultimately mutagenesis [332, 333], which is the first step for development cancer. Due to their antioxidant properties, xanthophylls have many applications in nutraceutical, cosmetic and food industry. In the last years, these industries have used them as dietary supplement to treat or prevent cancer (breast, colon, or endometrial…) and several inflammatory disorders. These natural products obtained from different organisms have been reported to be interesting molecules by its potent capacity to prevent or modulate colitis, cardiovascular disease, respiratory inflammation, thrombosis as well as enhance immune response in several *in vitro* and *in vivo* studies [334-337].

1. Astaxanthin

A lot of studies have reported important functions played by natural xanthophylls, including astaxanthin, in regulating immunity and disease aetiology.

Astaxanthin (Fig. 4B) has important applications in the nutraceutical, cosmetics, food and feed industries. Interest in the biological activity of astaxanthin, an oxyxarotenoid found in high amounts in the carapace of crustaceans and in the flesh of salmon and trout, has increased in recent years. Astaxanthin has several essential biological functions including protection against oxidation of essential polyunsaturated fatty acids; protection against UV light effects or immune response. In addition, *in vitro* studies have demonstrated that astaxanthin is several fold more active as a free radical antioxidant than β-carotene and α-tocopherol [314].

Some microorganisms such as the Chlorophyte alga *Haematococcus pluvialis* are rich in astaxanthin. This alga is believed to accumulate the highest levels of astaxanthin in nature and commercially grown *H. pluvialis* can produce 30 g of astaxanthin kg\(^{-1}\) dry

### Table 1 (Contd…)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Biologic Activity</th>
<th>Microalgae</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamins</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tocopherols</td>
<td>Antioxidant activity</td>
<td><em>Porphyridium</em></td>
<td>[420]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Spirulina platensis</em></td>
<td></td>
</tr>
<tr>
<td><strong>Phenolic compounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoic acid derivatives,</td>
<td>Antioxidant activity</td>
<td><em>Spiralina maxima</em></td>
<td>[421]</td>
</tr>
<tr>
<td>cinnamic acid derivatives and</td>
<td></td>
<td><em>Chlorella ellipsoidea</em></td>
<td>[421]</td>
</tr>
<tr>
<td>hydroxybenzaldehydes</td>
<td></td>
<td><em>Nannochloropsis sp.</em></td>
<td>[422]</td>
</tr>
<tr>
<td><strong>Volatile compounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phytol, neophtyadiene, etc</td>
<td>Antimicrobial and antioxidant activity</td>
<td><em>Synechocystis sp.</em></td>
<td>[423]</td>
</tr>
</tbody>
</table>

and cosmetic industry) and anti-proliferative properties (pharmaceutical industry). Bio-guided fractionation of microalgae extracts, followed by studies on human cells, have demonstrated that many pigments, beyond their ecological function as light harvesting molecules, also act as potent bioactive compounds on cancer cells and may have great potential in the prevention and treatment of cancers [317]. It has generated interest in many groups to purify original compounds, understand their biological activity, and also identify the pharmacological targets of molecules previously known for their ecological function.

### β-carotene

β-carotene (Fig. 4A) is the most studied and known carotenoid. It is ingested and processed in the liver and intestine to retinol, antioxidant component that favors the non-appearance of certain cancers as lung, breast, mouth and stomach. Currently, the most important marine source of β-carotene is *Dunalilla salina*, microalgae grown on large outdoor terrain in some countries like Israel, producing large amount for the market [318]. Epidemiologic studies indicate that an increased intake of fruits and vegetables that contain carotenoids as β-carotene and retinol is associated with a decreased risk of many types of cancer and degenerative diseases due to its antioxidant and anti-inflammatory activities [319-321].

Previous *in vitro* studies showed that β-carotene exhibited growth-inhibitory and proapoptotic effects in human colon adenocarcinoma cells, at least in part, by reduction in the expression of COX-2 [322]. In addition, data from animal models of colon carcinogenesis have shown that dietary supplementation of β-carotene reduced the number of ACF induced by AOM and colonic COX-2 expression [271].

The retinoids are a class of over 4,000 natural and synthetic molecules structurally and/or functionally related to fat-soluble vitamin A [323]. These compounds participate in a broad spectrum of biological activities, such as reproduction, embryogenesis, growth, differentiation, proliferation, apoptosis, vision, bone formation, metabolism, hematopoiesis and immunological processes [324]. Several studies have demonstrated the important role of vitamin A and retinoids in the oncogenesis of many tissues. In 1995 Lotan [325] showed, through *in vitro* and *in vivo* applications, that these compounds can influence malignant cell growth in a number of ways, by producing growth arrest and apoptosis, in a variety of cell lines [326].

### Xanthophylls

Xanthophylls are yellow or brown pigments belonging to the carotenoids group, and they were first isolated from crab *Astacus astacus*. They are also found in plants, yeast, trout, salmon and shellfish, feathers of some birds and specially, in microalgae.
biomass [338]. Currently, microalgae as H. pluvialis suppose an important source of astaxanthin and relative-molecules, which are used for preventing inflammatory process, such as colitis, and some types of cancer, including colon cancer [314, 339, 340]. In this regards, dietary astaxanthin ameliorated the colonic inflammation induced by DSS. These beneficial effects were due to the reduction of the inflammatory factors TNF-α, IL-1β, COX-2 and NF-xB [341].

Previous in vitro studies reported that this compound exhibited growth-inhibitory effects by arresting cell cycle progression and promoting apoptosis in a number of colon cancer cells, including HCT-116, HT-29, LS-174, WiDr and SW-480 [314]. Astaxanthin has also been described to reduce AOM/DSS-induced colorectal carcinogenesis in mice though inhibition of TNF-α, IL-1β and NF-xB expression as well as by suppressing proliferation and inducing apoptosis in the colonic adenocarcinomas [341]. In addition, this natural product stimulated apoptosis in DMH-induced rat colon carcinogenesis through the regulated expressions of NF-xB, COX-2, MMP-2 and 9, proliferating cell nuclear antigen (PCNA) and ERK-2 [342].

The anti-inflammatory and antioxidative effects of astaxanthin has also been showed in a randomized double-blind, placebo-controlled study. This natural product enhanced immune response, and decreased oxidative status and inflammation in young healthy women [343].

2. Lutein

Lutein (Fig. 4C) is an important xanthophyll known by its potent antioxidant activity, being the second most prevalent carotenoid in human serum [344], and dark, leafy green vegetables such as spinach and kale are the major lutein sources in food [345].

Like other carotenoids, the protective effects of lutein are linked to its ability to act as an antioxidant, because it is a potent quencher of singlet oxygen molecules and an excellent direct free radical scavenger [346]. For instance, lutein has been recommended for cancer prevention and diseases related to retinal degeneration [347, 348]. Moreover, this compound has shown protective effects against the development of early atherosclerosis [349].

Several epidemiological and experimental studies have reported that lutein could be used as a dietary supplement for reducing injury in tissues by antioxidant and anti-inflammatory pathways. This compound may protect against alterations of the redox status, DNA damage and inflammatory process by ROS-mediated induction. ROS are closely related to both cancer and the inflammatory process by family of oxidant-sensitive proteins, such as transcriptional modulator NF-xB [350]. It has been showed that several mycotoxins, for example deoxynivalenol (DON), generate free radicals that induce lipid peroxidation and cellular redox signalling, leading to changes in membrane integrity and in the antioxidant status of the cell. A recent in vitro study on a human colon adenocarcinoma cell line (HT-29) showed the cytoprotective effect of lutein on DON-induced oxidative stress and inflammation, through a reduction in oxidative stress, by maintaining glutathione levels, inhibition of nuclear migration of NF-xB, downregulation of COX-2 expression and prevention of apoptosis [351]. These antioxidative actions of lutein have been also recently evaluated in a human derived liver cell line (HepG2) using cisplatin as a control. It was showed that cisplatin induced pronounced oxidative stress related to DNA damage and that the supplementation with lutein protected these adverse effects caused by the exposure of the cells to platinum compound [352]. Moreover, lutein has been reported to inhibit hydrogen peroxide-induced activation of NF-xB and IL-8 expression in gastric epithelial AGS cells [353]. It has been also shown that a balance of dietary lutein and PUFAs may reduce the inflammatory process through PPARs pathways, IL-1 and retinoic acid X receptor (RXR) in chickens [354].

High lutein intake is associated with a reduction in cancer risk including colon or pancreas cancer [355, 356]. In vivo studies have recently shown that dietary supplementation of lutein reduced colon carcinogenesis in rats by modulation of proteins involved in cellular proliferation, including K-ras, the protein kinase B (PKB) and β-catenin [357]. In addition, another paper reported that the chemopreventive activity of β-carotene and lutein against colon carcinogenesis depends on the dose level. In this way, low doses of β-carotene and lutein inhibited AOM-induced rat colonic ACF formation but high doses augmented ACF incidence [358].

Some marine microalgae as Chlorella ellipsoidea and Chlorella vulgaris have showed to have anti-proliferative effects on a human colon cell line (HCT-116) by early apoptosis induction. This effect was due to their vast content in carotenoids, although the main of them was lutein [326]. For this reason, microalgae could be a lutein alternative source by biotechnological advances [339].

3. Violaxanthin

Violaxanthin (Fig. 4D) is a natural xanthophyll pigment with an orange colour found in a variety of plants, macro- and micro-algae. This product has been isolated from several microalgae including Dunaliella tertiolecta. Recently, this microalgae has been chemically investigated to isolate molecules inhibiting cancer cell proliferation and inducing apoptosis in MCF-7 (breast) and LNCaP (prostate) cancer cell lines.

In this study, violaxanthin showed strong antiproliferative activity by inhibiting cancer cell proliferation and inducing apoptosis on MCF-7 cell line [313]. An extract of Chlorella ellipsoidea containing mainly violaxanthin exerted strong antiproliferative effects, including induction of apoptosis in HCT-116 human colon cancer cells [326]. These results suggest that studying the pharmacology of violaxanthin and pharmacomodulated derivatives on cancer cells and in vivo models may allow potent antiproliferative drugs. Moreover, currently many groups are studying how to increase violaxanthin from microalgae production taking advantage of their easy culture using nuclear transformation or UVA mediated modulation of photosynthetic efficiency for producing high amount [360].

Poly sacchari des

Polysaccharides are natural polymers with a variety of properties that may be translated into significant commercial applications. Marine microorganisms, such as bacteria or microalgae, are considered a vast source of polysaccharides due to the enormous marine diversity. Since 1990’s, polysaccharides from microalgae have been studied because of their structural diversity, which leads to a wide diversity of applications such as in vitro inhibition of viral replication [361, 362]. More recently, they have been reported to possess many biological activities, such as antiviral, antitumor, antimicrobial, anticoagulant [363] and immunomodulating effects. These compounds are susceptible to be modified chemically in order to tailor new properties and hence to broaden the spectrum of potential applications. A recent paper has reported the structural determination of a cell wall glycoprotein from the red microalga Porphyridium sp. [364]. The additional importance of this research lies in its potential for biotechnological applications, especially in evaluating the use of microalgae as cell factories for the production of therapeutic proteins.

Microalgae have recently gained increasing interest as bioreactors for recombinant protein production, for example, overexpression of the phytoene synthase gene from the green algae Chlorella zogligenis in Chlamydomonas reinhardtii led to a two-fold increase in the content of violaxanthin and lutein [360] which are very interesting in the antioxidant and antiinflammatory process. Proteins from microalgae are interesting because has been showed to have immune modulating activities. In this line, bioactive phycocyanin and water soluble polysaccharides of Spirulina are responsible for its enhanced biological defense activity against infectious
diseases and reduction of allergic inflammation through sustaining the functions of the mucosal immune system. However, use of polysaccharides is restricted for various reasons, including a lack of simple methods for isolating them from extracts. Despite several methods for isolation of seaweed polysaccharides have been reported, all of them are rather labour intensive and time consuming.

In 2001, Pugh et al. [365] reported that immulina, a high-molecular weight polysaccharide fraction from *Spirulina*, was a potent activator of NF-kB and induced both IL-1β and TNF-α mRNAs in THP-1 human monocytes. Balachandran et al. [366] showed that immulina derived from *Spirulina platensis* activated monocytes THP-1 and NF-kB through a CD14- and TLR2- (receptors which recognizes pathogens and active innate immunity) - dependent process. On the other hand, in an *ex vivo* experiment, spleens and Peyer’s patches from mice fed with immulina showed an IgA production enhanced in Peyer’s patch cells and similarly, IFN-γ production was enhanced in cells isolated from the spleens of mice consuming the *Spirulina* extract [366].

For this reason, science is developing biotechnological transformation methods of microorganisms such as microalgae, to use them as pharmaceutical bio-factories [367-370].

**Fatty Acids**

Fatty acids are considered an important source of biological components for the treatment of several pathologies, much of them inflammatory diseases, including IBID, atherosclerosis, Parkinson’s and Alzheimer’s diseases and cancer. From a chemical point of view, many of these compounds are long chain fatty acids where they can be either saturated or unsaturated, PUFAs being the most studied for their pharmacological potential. Data from epidemiological, clinical and experimental studies have reported that dietary fish oil containing n-3 PUFAs have benefits for human health, including protection against colon cancer development and other cancers such as endometrial, breast and prostate cancer [371-373]. Fish oils are the main sources of n-3 PUFAs because of their high levels of docosahexaenoic acid (DHA) (Fig. 4E), eicosapentaenoic acid (EPA) (Fig. 4F) and docosapentaenoic acid (DPA). However, their clinical use is often limited by their unpleasant fishy taste and its adverse effects such as flatulence, halitosis, heartburn, diarrhoea and belching [374, 375].

Since there is a high demand for n-3 PUFAs in the pharmaceutical and food industries, alternative processes for PUFAs production are currently being studied, as for example exploitation of microalgae [376]. The marine environmental and specially microalgae are a huge source of different fatty acids, including monoun-saturated fatty acids, such as oleic acid (OLA) and PUFAs, including linoleic acid (LNA), α-linoleic acid (ALA), EPA and DHA. Among them, EPA and DHA are the major PUFAs in microalgae. Moreover, conjugated linoleic acid (CLA) is common in cooked meat, pasteurized dairy products or processed cheeses. It has been shown that microalgae can modulate the CLA content; in this line, *Spirulina platensis* extract [366], eicosapentaenoic acid (EPA) (Fig. 4F) and docosapentaenoic acid (DPA). However, their clinical use is often limited by their unpleasant fishy taste and adverse effects such as flatulence, halitosis, heartburn, diarrhoea and belching [374, 375].

A promising avenue for developing such immunonutrition-based therapies for IBID is by targeting PPAR-γ. Moreover, the anti-inflammatory mechanisms of fatty acids have been shown to be related, in part, to their regulatory effect on PPARs. PPAR-γ has been shown to produce beneficial effects in experimental IBID by repression of NF-kB thereby reducing inflammation. At the same time, PPAR-γ interacts with NF-kB and modulates the intensity, duration and consequences of inflammation (Fig. 2) [381, 382].

As mentioned previously, the beneficial effects of PPAR-γ ligands in both human and animals suffering from colitis has been previously demonstrated. At present, there is a need to discover novel naturally agonists of PPARs that exert therapeutic and prophylactic actions against inflammatory disorders, with limited side-effects. Fatty acids are known to bind to PPAR-γ, having PUFAs higher binding affinity than saturated or monounsaturated fatty acids [383]. In this line, our research group is currently working on PUFAs isolated from microalgae. These compounds, called oxilipins, have shown to have an interesting anti-inflammatory activity *in vitro* by decreasing TNF-α production and their action may be due, in part, to the regulation of PPAR-γ and NF-kB pathway [384].

In animal models of IBID, a large body of evidence supports a protective effect of PUFAs through PPAR-γ-dependent mechanisms. Along these lines, CLA induced colonic PPAR-γ expression and provided protection against the disease in a pig model of bacterial-induced colitis [385], as well as in mouse and pig models of DSS colitis [36, 37]. Similarly, DHA and EPA diet administration attenuated colonic mucosal inflammation in rats; this effect was associated with reduced levels of kBoB/β and high PPAR-γ expression [386]. A recent study has reported the anti-inflammatory activity of EPA in IL-10 gene-deficient mice through the PPAR signaling pathway [387].

In addition to PPAR-γ modulation, other mechanisms by which PUFAs exert their beneficial effects in colitis have been described. In this respect, dietary olive oil administration supplemented with EPA and DHA in rats with DSS-induced colitis reduced colonic inflammatory response through the reduction of levels of leukotriene B(4), TNF-α and NO [388]. Interestingly, the same diet combined with quercitrin caused a significantly greater inhibitory effect of the proinflammatory mediators in comparison with rats receiving the diet without this flavonoid. These effects were also associated with a lower colonic iNOS and COX-2 expression [389]. In addition, oral administration of pure DHA in BALB/c mice with colitis ameliorated the inflammatory changes of the colon through downregulation of inflammatory cytokines such as IL-1β, CD14 antigen and TNF-α, as well as membrane remodeling genes such as MMP-3, -10 and -13 [390]. Varnalidis et al. [391] have recently reported that animals fed a diet containing high levels of EPA exhibited a reduction in colonic epithelial erosion after 8 days of DSS-induced colitis despite the increased colonic neutrophil infiltration. The preventive effects of these compounds have also been shown in human studies. Along these lines, a prospective cohort study reported that dietary intake of the n-3 PUFAs EPA and DHA, was associated with protection from colitis in a cohort aged over 45 years [392].

On the other hand, PUFAs have been reported to have beneficial biological functions in carcinogenic processes. *In vitro* studies have demonstrated that EPA and DHA induced apoptosis in the colon cancer cell lines HT-29, Caco-2, and DLD-1 through an increase in caspase-3 activity and inhibition of Bcl-2 [393]. In addition, the antiproliferative properties of oils containing EPA and DHA, derived from three microalgae (*Crypthecodinium cohnii*, *Schizochytrium* sp. and *Nitzschia laevis*), have been previously shown in human colon adenocarcinoma Caco-2 cells [378]. These n-3 PUFAs also suppressed cell growth and VEGF expression in HT-29 cells cultured *in vitro* as well as *in vivo* when implanted in nude mice. The anti-angiogenic properties of these fatty acids were
due in part to the downregulation of the COX-2/PGE\textsubscript{2} pathway [394]. Another study reported that lycopene and EPA synergistically inhibited the proliferation of human colon cancer HT-29 cells by downregulation of PI3K/Akt/mTOR signaling pathway [395]. Allred \textit{et al.} [396] found that growth inhibitory effects of EPA in these cells were the result of a PPAR\gamma-mediated pathway. DHA depressed colon tumor growth \textit{in vitro} through p53 dependant-apoptosis and p53 independent pathways. In addition, these authors reported an inhibition of the growth of human adenocarcinoma COLO 205 in nude mice by a diet supplemented by golden algae oil containing DHA [397].

Further experiments in animals have shown that chemical induction of colon tumors by AOM or DMH in rats decreased when the animals were fed diets containing DHA and EPA [398-400]. In 2009, van Beelen \textit{et al.} [401] studied the chemopreventive effects of high fat microalgal oil diet on AOM-induced colon carcinogenesis in rats following eight weeks of dietary treatment. These effects were compared to the effects of high fat fish oil. The results showed that both these oils gave the same 50\% reduction of AOM-induced ACF when compared to corn oil, suggesting that microalgal oil is a good alternative for fish oil regarding protection against colorectal cancer. Another study reported that EPA diet administration caused a significant suppression of polypl number and growth in Apc\textsuperscript{Min} mice. This effect was associated to a significant reduction in COX-2 expression and \beta-catenin nuclear translocation [402].

The chemopreventive efficacy of EPA in patients with familial adenomatous polyposis (FAP) has been recently reported in a randomised, double-blind, placebo-controlled trial. Treatment with this fatty acid for six months reduced the polyp number and the sum of polyp diameters, showing a favorable safety profile [403]. In another study, supplementation with EPA (2 g/day for 3 months) significantly increased apoptosis and reduced cell proliferation in normal colonic mucosa in patients with colorectal adenomas [404]. Therefore, the marked inhibitory effect of these PUFAs on cancer development, in the absence of toxicity, makes these fatty acids excellent candidates for both CRC chemoprevention and treatment.

CONCLUSION

Clinical and epidemiologic studies have suggested a strong association between chronic infection, inflammation and cancer. In this regard, intestinal neoplasias, originated under chronic inflammatory conditions have been the object of numerous studies in both humans and animals, and the association between IBD and elevated risk for CRC was established.

There are two different pathways linking inflammation and tumorigenesis: an extrinsic pathway mediated by chronic inflammatory and oxidative environment (inflammation-cancer) and an intrinsic pathway in which genetic alterations induce alterations in cell cycle and proliferation, apoptosis, or metastatic and angiogenic effects and in the absence of an underlying inflammation, initiate a tumour-driven host immune response leading to a microenvironment composed of inflammatory cells (cancer-inflammation). These data suggest that inflammatory response represent a basic mechanism for cancer origin and development.

Numerous \textit{in vitro} and \textit{in vivo} studies and some clinical data have well established the antioxidant, anti-inflammatory and anti-cancer potential of the dietary nutrients from plants and from microorganisms such as microalgae. In this line, the simple growth requirements of microalgae make them attractive for demand by the pharmaceutical, food and cosmetic industry. Complementary basic
studies and well-controlled randomized clinical trials are required to ascertain the optimal dose for chemopreventive efficacy, excluding toxic effects, all with the objective to be validated for a good clinical practice.

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflicts of interest.

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**REFERENCES**


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Jaiswal AS, Marlow BP, Gupta N, Narayan S. Beta-eaten-mediated transactivation and cell-cell adhesion pathways are impor-


Gupta SC, Kim JH, Kannappan R, Reuter S, Dougherty PM, Aggarwal BB. Role of nuclear factor kB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutri-

Plummer SM, Holloway KA, Manson MM, et al. Inhibition of cyclo-oxygenase-2 expression in colon cells by the chemopreventi-


Martin D, Galisteo R, Gutkind JS. CXC8/LIL8 stimulates vascular endothelial growth factor (VEGF) expression and the autocrine ac-

Wang X, Wang Q, Ives KL, Evers BM. Curcumin inhibits neuro-

Zhang F, Altorki NK, Mestre JR, Subbaramaiah K, Dannenberg AJ. Curcumin inhibits cyclooxygenase-2 transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial cells. Carci-

Goel A, Boland CR, Chauhan DP. Specific inhibition of cyclo-


Du B, Jiang L, Xia Q, Zhong L. Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon can-

Su CC, Chen GW, Lin JG, Wu LT, Chung JG. Curcumin inhibits cell migration of human colon cancer cell 205 cells through the in-
bihition of nuclear factor kappa B/p65 and down-regulates cycloo-

Binion DG, Otterson MF, Rafiee P. Curcumin inhibits VEGF-

Li L, Ahmed B, Mehta K, Kurzrock R. Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angi-


Senda T, Izuaka-Kogo A, Onouchi T, Shimomura A. Adenomatous polyposis coli (APC) plays multiple roles in the intestinal and colo-

Mahmoud NN, Carothers AM, Grunberger D, et al. Plant phenolics decrease intestinal tumors in an animal model of familial adenoma-


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Fini L, Pizzaghi G, Ceccarelli C, et al. Highly purified eicosapentaenoic acid as free fatty acids strongly suppresses polyps in Apc(Min+/+)


Mendes RL, Nobre BP, Cardoso MT, Pereira AP, Palabra AF. Supercritical carbon dioxide extraction of compounds with pharmaceutical importance from microalgae. Inorg Chim Acta 2003; 356: 328-34.


