

EUROMEDITERRANEAN BIOMEDICAL JOURNAL

for young doctors

Review

INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER, NUTRACEUTICAL ASPECTS.

**Margherita Mazzola (1*), Francesco Carini (1*), Angelo Leone (2*),
Provvidenza Damiani (3*), Abdo Jurjus (4*), Alice Geroges Geagea (2,4*),
Rosalyn Jurjus (5*), Tarek Bou Assi (6*), Eleonora Trovato (7*),
Francesca Rappa (1,7*) Giovanni Tomasello (1,7*)**

*** These Authors share the first autorship.**

Summary

Nutraceuticals constitute a group of functional foods that provide added health benefits for various disorders including inflammatory bowel disease (IBD) and colorectal cancer (CRC). The main groups of nutraceuticals include probiotics, prebiotics, omega 3 and antioxidants. Studies on Nutraceutical showed that this type of food possessed similar proprieties to drugs but with the benefit of not having side effects.

This mini review shows that probiotics and prebiotics, when administered simultaneously with traditional therapies, reduce IBD symptoms and reduce synthesis of enzymes probably involved in colorectal carcinogenesis. Moreover, Omega 3 reduces the synthesis of inflammation mediators and prevents carcinogenesis through interaction with the signaling pathway NOTCH1/MMP9. Moreover, antioxidants reduce the inflammatory process by inhibiting the synthesis of inflammatory mediators, and inhibit the mechanisms of cell proliferation by inducing apoptosis.

In brief, nutraceuticals have gained a huge clinical interest since they could be used along with traditional therapy. Bioavailability studies of nutraceutical supplements guarantee a correct intake of the substance by oral administration, a matter which would not have been possible to have entirely with the consumption of regular food only.

Address of the authors:

- 1) Department of Experimental Biomedicine and Clinical Neuroscience, Section of Human Anatomy, (BIONECA), University of Palermo, Italy.
- 2) Department of Experimental Biomedicine and Clinical Neuroscience, Section of Histology, (BIONECA), University of Palermo, Italy.
- 3) AOUP "P. Giaccone", School of Medicine and Surgery, University of Palermo, Italy.
- 4) Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut (AUB), Beirut, Lebanon.
- 5) Department of Anatomy and Regenerative Biology, School of Medicine and Health Sciences, George Washington University, Washington D.C., USA.
- 6) Department of Laboratory Medicine, Psychiatric Hospital of the Cross, Jal eddib, Lebanon
- 7) Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

Send correspondence to: Giovanni Tomasello giovanni.tomasello@unipa.it

Received: 27th July, 2016 — **Revised:** 28th August, 2016 — **Accepted:** 13th September, 2016

Introduction

Nutraceutical, a “portmanteau” of the words “nutrition” and “pharmaceutical”, is a term used to describe specific foods that provide extra health benefits in addition to their basic nutritional value. Various studies conducted on nutraceutical products found that this particular type of foods have similar properties to some medications with the benefit of having no side effects. Moreover, recently, investigators started combining traditional medical therapy with various nutraceutical foods in order to reduce medications side effects.

The aim of this article is to highlight the importance of some nutraceutical products, such as probiotics, prebiotics, essential fatty acids and antioxidants, in preventing and treating some disorders, especially, inflammatory bowel diseases (IBD) and colorectal cancer (CRC).

IBD and CRC

IBD's are chronic bowel disorders that include ulcerative colitis (UC), Crohn's disease (CD) and Indeterminate Colitis (1-3). UC affects primarily the last part of the intestine (colon and rectum) while CD may affect any part of the gastrointestinal tract from mouth to anus, with a characteristic abrupt transition between unaffected and inflamed mucosal areas (2,4).

On the other hand, CD is characterized by a transmural pattern of inflammation with alternating periods of remission and flare up that often cause the formation of fistulae, abscesses and stenosis. UC, instead, affects the mucosa with frequent erosions and bleeding (1,4,5). Both disease entities have similar symptoms such as diarrhea (sometimes mucus-like and with blood), abdominal pain, nausea, fatigue, anemia and weight loss (3,5).

The pathogenesis of IBD is multifactorial. It involves alterations in the composition of the intestinal microbiota (process known as dysbiosis that seems to be the “*primum movens*” for the genesis of IBD), alterations in the immune response, genetic (for example the alteration of NOD2 genes) and environmental factors (physical and psychological stress, surgery, cigarette smoking and

diet) (2-4).

The resulting inflammation and dysbiosis may also predispose the individual to the onset of colorectal cancer. Colorectal cancer is the third most common cancer in the world following lung cancer and breast cancer (6-8). Its onset, not yet fully clarified, could be linked to various factors including genetic (only in 20% of cases), environmental (exposure to pollutants, inflammatory bowel disease, etc.) and lifestyle (physical inactivity, diet high in fat and sugar, regular consumption of alcoholic drinks and smoking) (8). All of these factors promote an increased oxidative stress and reactive oxygen species (ROS) (6,9) while maintaining the chronic inflammation of the colonic mucosa.

In turn, the ROS and chronic inflammation cause alterations at the DNA level (aneuploidy, chromosomal and genetic instability, punctiform mutations, insertions and deletions) which could promote the appearance of dysplastic lesions in the colon and subsequent colorectal cancer (7-9).

In addition, ROS could function as cellular messengers by stimulating the production of pro-inflammatory cytokines, cell motility and angiogenesis that increase the supply of oxygen, nutrients and growth factors to the healthy and tumor cells (10).

Probiotics

Probiotics are mixtures of bacteria (mostly *Lactobacilli*, *Bifidobacteria* and *Enterococci*) (11,12), which are normally found in the intestine but which can be reduced like in dysbiosis (12).

The importance of probiotics to the health of the human gut has been well documented over the years. These bacterial strains are able to perform various functions such as:

- a) Preventing the proliferation and adhesion of pathogenic bacteria to the intestinal lumen (13);
- b) Increase the resistance of cell junctions, and thus reducing the permeability of the colonic mucosal barrier by modulating the gene expression of proteins involved in these junctions (14);
- c) Increase the viscosity of mucus cover-

ing the colonic mucosa, thus preventing the colonization of pathogenic bacteria (13).

Probiotics also have a beneficial effect on the intestinal immune system and inflammation because they are capable of increasing the production of IgA, defensins and bacteriocins in the colonic lumen. Also, probiotics reduce the proliferation of pathogenic bacteria and the synthesis of inflammatory cytokines by down regulating the genes involved in the synthesis of these cytokines, particularly, NF- κ B and its ligand I κ B, which remain sequestered in the cytoplasm (14).

Prebiotics

Prebiotics are non-digestible fiber compounds found in some plants as carbohydrates. Prebiotics stimulate the growth and activity of advantageous bacteria that colonize the colon by acting as substrate for them. The most well-known prebiotics are inulin and oligofructose, which are digested by *Lactobacilli* and *Bifidobacteria* in the gut flora leading to the reduction of short chain fatty acids (SCFAs): butyric acid, acetic acid and others. These SCFA's, mainly butyric acid, transported to colonocytes, suppress the survival of colonic adenoma and cancer cells (15). Dietary fiber is fermented by microbes into butyrate inside the lumen of the colon and the butyrate is then transported into the colonocytes (15).

Prebiotics are involved in various processes such as the proliferation, differentiation and apoptosis of colonic cells. They have an anti-inflammatory effect and promote resistance to colonization by pathogenic bacteria (1,15). Butyric acid also strengthens the defensive barrier of the colon by increasing the production of mucins and antimicrobial peptides, and by decreasing the intestinal epithelial permeability through increasing the expression of the tight junctions proteins (1).

Omega 3

Omega - 3 (ω 3) fatty acids, also called polyunsaturated fatty acids (PUFAs), are considered essential lipids. Because the body is unable to produce them and for this reason they should be introduced

with the diet. They are found in some plants oils (such as edible seeds, walnuts, flaxseed and other vegetable oils), and in some animals such as fish oils, squid oils and salmon (5,16).

PUFA have several benefits on the human organism, they reduce blood triglycerides levels, modestly lower blood pressure and improve inflammatory processes (17). The anti-inflammatory actions of PUFA, when administered orally in the form of supplements, are expressed at different levels:

- a) Reduction of the chemotaxis of neutrophils and monocytes to the inflammatory site by inhibiting the synthesis of chemoattractants;
- b) Reduction or inhibition of the eicosanoids synthesis by inhibiting arachidonic acid metabolism;
- c) Decrease of T lymphocytes reactivity by inhibiting the production of interleukin - 2 (IL-2) and the proliferation of T cell populations;
- d) Reduction of production of inflammatory cytokines by down-regulating the expression of genes responsible for the production of these cytokines;
- e) Downregulation of the expression of genes encoding adhesion molecules, and thus reducing the interaction between leukocytes and endothelium (16).

Antioxidants

Antioxidants are substances capable of reducing oxidative stress due to their ability to bind and neutralize reactive oxygen species (ROS). Polyphenols, the main class of antioxidants, can be found in various foods such as fruits, vegetables, cereals, tea, coffee and red wine (18). Once ingested, polyphenols are processed and metabolized by the intestinal microbiota. They possess several beneficial effects such as modulation of the immune response, improvement of cell-cell signaling and tight junction barrier, reduction of oxidative stress and bowel inflammatory processes (18,19).

Polyphenols include different types of antioxidants such as anthocyanins, that give vegetables and fruits their rich colors (20, 21), Anthocyanins, such as the catechins (found mainly in green tea), tocopherols (also known as vitamin E, found in vegetable oils) (22), and res-

veratrol (found in the peel of red grapes and consequently in red wine) (23). Other dietary antioxidants includes α and β carotene (found in carrots, orange and yellow fruits, and vegetables), lycopene (found mainly in tomato), lutein and zeaxanthin (found in green plants) (24).

Discussion

Currently, the use of nutraceuticals to treat IBD symptoms is a very interesting and up-to-date subject of discussion, especially regarding the use of omega 3 as an anti-inflammatory agent and probiotics for restoring the balance of the intestinal bacterial flora. Nutraceutical products, through the use of antioxidants and anti-inflammatory substances, may prevent the development of dysplastic lesions in the colon and subsequent colorectal cancer.

The main active nutraceuticals and their effects on IBD and CRC are summarized in Table 1.

Numerous studies showed that an oral supplementation with probiotics improves the inflammatory process in IBD. *Lactobacillus Rhamnosus* strain is capable of reducing the synthesis of some

inflammatory mediators involved in IBD (13), such as NF- κ B (13) and TNF- α (10), and increases the production of immunoglobulins by intestinal cells (for example IgA) (12). *Bifidobacteria* have also an immunomodulatory action, especially on CD4⁺ lymphocytes (13).

Tomasello et al. showed that probiotics when given to patients, mainly *Lactobacillus Rhamnosus GG*, inhibited the activity of certain enzymes compared to the placebo group (13). The concomitant administration of *Lactobacillus casei* and *Bifidobacterium lactis* in animal models with induced colitis, reduced the extent of the inflammatory reaction in the colonic mucosa, improved all cellular features of malignancy, thus proving that probiotics may have a possible role in preventing CRC (14).

Other studies showed that mixtures of probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) help in improving the inflammatory status of the colon mucosa (12) by down-regulating the expression of some inflammatory cytokines, such as IL-6, IL-1, IL-8 and TNF- α (13,14).

Nutraceuticals	Effects on IBD	Effects on CRC
Probiotics	<ul style="list-style-type: none"> - Reduction of the synthesis of inflammatory mediators; - Increased production of immunoglobulins; - Immunomodulation. 	<ul style="list-style-type: none"> - Reduction of the synthesis of enzymes probably involved in colorectal carcinogenesis; - May reverse the cellular features of malignancy
Prebiotics	<ul style="list-style-type: none"> - Increased butyrate synthesis; - Modulation of intracellular pH. 	<ul style="list-style-type: none"> - Reduction of cancerous cells proliferation; - Restore apoptosis in cells with uncontrolled proliferation.
Omega 3	<ul style="list-style-type: none"> - Reduction of the synthesis of inflammatory mediators; - Improvement of inflammatory symptoms 	<ul style="list-style-type: none"> - Counteract the inflammatory effect; - Prevent carcinogenesis through interaction with the signaling pathway NOTCH - 1/ MMP9.
Antioxidants	<ul style="list-style-type: none"> - Reduction of inflammatory processes; - Inhibition of the synthesis of inflammatory mediators. 	<ul style="list-style-type: none"> - Reduction of oxidative stress; - Inhibition of cellular proliferation mechanisms; - Induction of apoptosis.

Table 1: Main active nutraceuticals and their effects on IBD and CRC

Moreover, patients treated with prebiotics had similar improvements in IBD symptoms. Patients with CD when treated with prebiotics (5) had an increase in the production of SCFAs, and particularly butyric acid. This substance is capable of modulating the intracellular pH of colonic cells, regulating the gene expression and the proliferation of colonic epithelial cells, and inhibiting DNA synthesis by activating apoptosis in rapidly proliferative cells, and thus preventing the onset of colorectal cancer (15).

In IBD, the administration of ω 3-PUFA reduces the damage and the inflammatory reaction at the colonic mucosa by reducing the production of eicosanoids from arachidonic acid derivatives (16), and through their metabolization to 3-series prostaglandins and 5-series thromboxane and leukotriene (1).

Also, ω 3-PUFA exert their anti-inflammatory activity through the down-regulation of several mechanisms including the chemotaxis of lymphocytes, the expression of adhesion molecules, the reactivity of T-helper lymphocytes and the reactivity of colonic cells by changing the composition of the cell membrane which causes transcriptional activation of peroxisome proliferator activated receptor (PPAR) γ . Furthermore, ω 3-PUFA serves as a substrate for the synthesis of proteins that help in reducing the inflammatory reactions such as resolvin, protectin and maresin (17).

Studies performed on the Eskimo population, largest consumer of ω 3-PUFA, showed a very low prevalence of IBD in the population, suggesting that these fatty acids may play an important role in the prevention of IBD (5).

It is noteworthy that ω 3-PUFAs may play an important role in colorectal carcinogenesis. Fazio et al. demonstrated in mice having colon cancer associated with colitis (CAC), that ω 3-PUFA interact with the signaling pathway NOTCH-1/MMP9. This signaling pathway is linked to the progression of the carcinogenesis process, through an up-regulation of NOTCH-1 and MMP9 resulting from the ongoing inflammatory reaction (25).

Furthermore, several studies supported the use of antioxidants, especially epigallocatechin-3-O-gallate (EGCG) (that we

find in green tea) and theaflavin 3,3'-digallate (that we find in black tea), in the treatment of IBD (mainly in animals models with induced colitis). They showed how these substances were able to inhibit various inflammatory signaling pathways such as those mediated by $\text{NF-}\kappa\text{B}$, I κ B α and IKK (26,27), with reduced production of inflammatory cytokines (such as IFN- γ , IL-12, TNF- α , and iNOS myeloperoxidase) (26,27). They also showed that there was not only a reduction of inflammatory processes, but also a reduction in symptoms such as diarrhea and weight loss (26).

In addition, EGCG can also stimulate and enhance the synthesis of glutathione (GSH), one of the most potent antioxidants present in our body, which is capable to bind and neutralize ROS, thus reducing cellular damage and preventing the process of carcinogenesis (28).

Among the polyphenols, anthocyanins have been shown to inhibit tumor growth in experimental models of mice. This inhibition can be explained by several mechanisms: arrest of the cell cycle, induction of apoptosis, induction of anti-proliferative mechanisms, reduction of oxidative stress, reduction of inflammatory mechanisms or by their action on demethylation mechanisms of tumor suppressor genes (29-31). Likewise, tocopherols exhibit an anti-cancerous activity by reducing inflammation and by inducing apoptosis (32).

For the carotenoids, the action of β -carotene on colorectal cancer cells was also investigated. It was shown that these substances reduce the activity of an enzyme involved in the increased synthesis of metalloproteinase responsible of tumor invasiveness (33). It is also important to note that resveratrol exerts an action on colorectal cancer cells by blocking the up-regulation of K-ras and consequently tumor growth (34).

Conclusions

This mini review has shown that there is a growing interest in these functional foods. It is clear that many studies are still needed since most of them included only animal models or cell cultures. In brief, nutraceuticals have recently gained

a huge clinical interest since they could be used simultaneously with traditional therapy but with the benefit of not having any side effects. In addition, nutraceuticals have gained some economical interest because pharmaceutical companies have started the production of these supplements on a large scale.

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