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LETTER TO THE EDITOR

**COLORECTAL CANCER AND INFLAMMATORY BOWEL DISEASES:
EFFECTS OF DIET AND ANTIOXIDANTS**

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It is well established that oxidative stress is common in inflammatory bowel diseases (IBDs). Accordingly, antioxidants are recommended for treatment. The aim of this study is to compare the effects of antioxidants contained in the various types of tea on symptoms and evolution of IBD and colorectal cancer (CRC). Analysis of the literature revealed that the theaflavin-3, 30-digallate (TFDG) contained in black tea, and epigallocatechin-3-O-gallate (EGCG) contained in green tea have protective effects against oxidative stress. Moreover, these substances are involved in many biochemical processes responsible for inflammation and proliferation of cancer cells. It is documented that both TFDG and EGCG are able to reduce inflammatory phenomena and symptoms associated with IBD, as well as to reduce the proliferation of CRC cells. Most studies are performed *in vitro* or in experimental animal models. It is, therefore, advisable to formulate studies that could be carried out on humans or human samples, in order to develop the appropriate therapeutic strategies.

To the Editor,

Inflammatory bowel diseases (IBDs) are a group of chronic idiopathic diseases which include ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (in this disease flogosis is limited to the colon, with histologic, clinical, and endoscopic characteristics that do not allow classification, as they are not attributable to CD or UC). In UC, the lesions are commonly located in the rectum and in the colon. In UC, the mucosa appears

hyperemic, bleeding and ulcerated with pseudo-polyps. On the other hand, CD may involve any part of the intestinal mucosa, from mouth to anus, with a typically segmental distribution of the lesions. IBDs have specific symptoms, characterized by abdominal pain, nausea, fever, fatigue, weight loss, and diarrhea, and nonspecific extra-intestinal symptoms such as arthritis, endocarditis, thyroiditis, alopecia, psoriasis, uveitis, and oral manifestations (1-3).

The etiology of IBD is multifactorial and involves

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a number of factors including dysbiosis, or alteration of the intestinal microbiota, genetic predisposition, deregulation of the immune response and dysfunction of the intestinal barrier with consequent alteration of permeability (1, 2).

The immune dysfunction mechanism involves activation of mucosa-associated lymphatic tissue (MALT) with the activation of the inflammatory cascade [leukocytes, cytokines, tumor necrosis factor- α (TNF- α)] and massive tissue damage (1, 2). In addition, the inflammatory mechanisms found in IBD are mainly related to mediators produced from nuclear factor kappa B (NF- κ B) transcription factor and by activator protein 1 (AP-1) (4). Moreover, there is also an involvement of nitric oxide (NO) through modulation of inducible nitric oxide synthase (iNOS) (4).

Another intestinal disease is colorectal cancer (CRC), which originates from a dysplasia of the colon cells. The dysplastic colocytes proliferate uncontrollably and cause adenomatous polyps which, if not removed, transform into cancerous polyps and colorectal cancer (1). Early lesions form aberrant crypt foci (ACF), defined as a set of polyps with abnormal lumina and thickened epithelium which are considered as micro adenomas (5). The sequence dysplasia - adenoma - carcinoma was well described in 1988, and is the result of a series of molecular events, such as inhibition of tumor suppressor genes, activation of oncogenes and modifications to the DNA, including changes of the state of methylation and mutations (1, 2).

Today, it is well known that colorectal cancer is a multifactorial disease; however, a common factor between IBD and CRC is oxidative stress. Reactive oxygen species (ROS) are known to be associated with many diseases as they can cause damage to DNA, cell membranes, proteins, and fatty acids (6). Oxidative stress is defined as a destruction of the balance between antioxidants and oxidative species. One of the oxidative factors is represented by ROS that originate from the processes of oxygen reduction which are represented by radicals such as superoxide anion, hydroxyl radical, peroxy, alcoxyl, hydroperoxy, and not by radicals including singlet oxygen, hydrogen peroxide and hydrochlorous acid (1, 2).

In patients with CRC, ROS causes alterations to DNA, for example, changes in the base pair GC (deletions, insertions, mutations) (7), microsatellite instability, and activation of oncogenic transcription factors such as AP-1, NF- κ B, and hypoxia inducible factor-1 (7); some of these factors are also involved in the inflammatory mechanism of IBD (1, 2, 7).

Today, given the great importance of oxidative stress and its relationship to diseases in many systems of the body, we tend to pay special attention to diet, food and drink which contain substances defined as "antioxidants", to be able to counteract the action of free radicals. One of the most documented antioxidant is tea represented by its different varieties. The focus of our analysis in this article is to compare the effects of antioxidants contained in the various types of tea on symptoms and evolution of IBD and CRC.

Tea antioxidants

Tea, after water, is the most widely consumed beverage in the world, especially in Eastern populations and recently also in Western populations (6). A study in the UK, the National Diet and Nutrition Survey on over 7,000 adults shows that 77% of people drink tea, with a mean consumption of 540 ml/day (about 2.3 cups) (8).

The scientific name of tea is *Camellia sinensis* L., belonging to the family *Theaceae*, native to South and South Eastern Asia. From this plant, different varieties of tea are obtained. They differ in respect to the time of leaf collection, leaf processing, geographic regions and growth conditions. Based on the first two conditions, one can distinguish between white tea, black tea and green tea.

White tea is unfermented, arising from young leaves or unopened buds. The leaves are harvested only once a year in spring. They are then steamed and dried, with minimal processing and oxidation (6). On the other hand, black tea is made from fermented and completely oxidized leaves. The third type, green tea, immediately after harvest, is subjected to a thermal process that inactivates the enzymes responsible for the oxidative processes, allowing the leaves to maintain their green color. This type of tea does not undergo fermentation or oxidation processes.

Black tea is the most consumed type of tea (80%

of the total tea consumption). It contains about 200 mg of flavonoids in each cup (2, 8). Particularly, black tea contains theaflavins (formed by oxidation of catechins during the working process of the leaves), such as theaflavin-3-gallate (TFD1) theaflavin-30-gallate (TFD2) and theaflavin-3,30-digallate (TFDG) (4, 8), as well as thearubigin (TG) and flavonoids such as quercetin, kaempferol, myricetin and rutin (8, 9).

Some studies carried out on mice, treated with trinitrobenzenesulfonic acid (TNBS) to induce experimental colitis, show how the polyphenols of black tea, in particular TFDG, are able to inhibit the production of NO and the mRNA of iNOS, also leading to a reduction in the levels of NF- κ B and a general reduction of inflammatory processes (4).

In contradistinction, green tea contains many antioxidant substances belonging to the family of polyphenols and, in particular, to the family of flavan-3-ol (commonly called catechins). The most important antioxidant compounds in this group are: (-) - epigallocatechin (EGC, 6 – 10% of total catechins), (-) – epicatechin (EC, about 2% of total catechins), (-) epigallocatechin-3-O-gallate (EGCG, 10 – 15% of total catechins), (-) - epicatechin - 3-O-gallate (ECG, 2 – 3% of total catechins), (+) - catechins and (+) - gallocatechin (5, 6, 10-12).

EGCG is the most abundant antioxidant in green tea (accounting for 30-40% of dried leaf extract, 200–300 mg per each cup of tea) (10-12), and is the one that shows the major antitumor properties. It has indeed been demonstrated that EGCG has the ability to induce apoptosis, to inhibit the proliferation of colon cancer cells, and to inhibit the formation of pre-neoplastic lesions (5). The mechanisms of action of EGCG are conducted through the induction of cell cycle arrest, and by inhibiting the activation of proteins such as mitogen-activated protein kinases, urokinase, lipoxygenase (1, 10), which are mediators of inflammatory processes such as cyclooxygenase (particularly cyclooxygenase 2 or COX-2) (13), receptors such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and growth factors such as human epidermal growth factor 3 (14).

Furthermore, EGCG is considered as an “epigenetic molecule” since it is capable of inducing epigenetic changes by inhibiting the activity of DNA

methyltransferase 1 (DNMT1) and modifying, in this way, the methylation status of the genes (15).

In brief, based on their polyphenolic structure, such substances in tea are powerful antioxidants. Their role against oxidative stress is expressed in different ways, such as chelate metal ions (for example Fe³⁺ free ions), thus preventing the formation of ROS, or reacting with reactive species such as NO, nitric dioxide, peroxy nitrite, superoxide radical, singlet oxygen and hydroxyl and, consequently, neutralizing their action (1, 2).

Through such activities, tea antioxidants protect cell membranes, DNA, lipids and proteins from the action of free radicals. It has been shown that drinking about three cups of tea per day, for at least two weeks, increases the concentration of flavonoids in the blood by at least 25%, leading to a greater protective effect against ROS (8). Furthermore, animal studies have shown that the polyphenols present in tea can modulate the composition of the intestinal microbiota by inhibiting the growth of the *Clostridium* bacterial strain and promoting that of *Bifidobacteria* (8).

Effects of tea antioxidants on colitis and IBD

The anti-inflammatory effect of tea polyphenols has been demonstrated using small animal models of IBD, (Balb-c wild type and interleukin-10-deficient mice with ulcerative colitis and enterocolitis, respectively) induced experimentally by administration of dextran sodium sulfate and exposure to normal microbiota or in mouse models with experimental colitis induced by administration of dinitrobenzene sulphonic acid (16).

The administration of EGCG and other polyphenols in green tea has improved and attenuated the symptoms in both experimental models, very much like the administration of sulfasalazine (16). In the same study, it was also shown that EGCG induces an increase of glutathione and has anti-inflammatory effects through inhibition of NF- κ B and I kappa B kinase (16). Furthermore, the administration of green tea extract improved symptoms such as diarrhea and weight loss. In addition, it ameliorated the damage derived from the destruction of the epithelium of the colon, and reduced the production of TNF- α and myeloperoxidase (MPO), thus reducing the inflammation (16).

However, the study by Ukil and co-workers demonstrated the protective effects of TFDG observed in experimental models of mice treated with trinitrobenzene sulfonic acid to induce experimental colitis. TFDG reduced tissue damage caused by inflammation by inhibiting the I κ B- α dependent signaling pathway. In particular, TFDG inhibited NF- κ B activation by inhibiting phosphorylation and subsequent degradation of I κ B- α , leading to a downregulation of the expression of genes such as interferon- γ , IL-12, TNF- α and iNOS, with consequent reduction in the production of inflammatory cytokines (4).

Effects of tea antioxidants on colorectal cancer

The beneficial effects of tea antioxidants have also been shown with regard to CRC. *In vitro* studies using white tea extract expressed antioxidant effects in 3T3-L1 cells subjected to oxidative damage by exposure to hydrogen peroxide. Furthermore, similar anti-cancer effects were shown in the HT-29 colon cancer cells; they were expressed through induction of apoptosis, as shown by increased levels of caspase 3, 7, 8 and 9 (6).

The anti-cancer effects of black tea extract (BTE) were also expressed in the HT29 cell line (human colon carcinoma cell line). BTE showed cytotoxic, antiproliferative, genotoxic effects and also induced cell apoptosis with a typical fragmentation of intranucleosomal DNA (9).

Furthermore, BTE reduced the formation and the number of ACF in male mice and inhibited the carcinogenesis process by modulating the activity of enzymes related to cell proliferation, such as cyclooxygenase, DNA polymerase and the protein kinase C (10).

In this respect, most studies have been performed on antioxidants in green tea. Studies on the Chinese population showed that regular consumption of green tea was associated with a significantly reduced risk of precancerous adenomas of colon and rectum. However, this effect could not be correlated only to the consumption of tea, but also to the diet rich in fruits and vegetables of the Eastern populations (17).

More specific studies conducted on EGCG catechins present in green tea showed that this

substance has an anti-proliferation activity in HT29 cells of colorectal cancer. Such antitumoral activity is expressed by inhibiting angiogenesis through the inactivation of extracellular signal-regulated kinases 1 and 2 (Erk-1 and Erk-2) and downregulation of mRNA expression of VEGF. However, the mechanism by which EGCG induces inactivation of Erk-1 and Erk-2 is not entirely clear (12).

Other studies have focused their attention on the association between EGCG and other substances and their combined effects on colorectal cancer. A study on prevention of CRC was conducted using the association between green tea and selenium. It has been observed that these two substances together prevent the formation of ACF through different genetic and epigenetic mechanisms, such as increased acetylation of histone H3, inhibition of the accumulation of nuclear β -catenin, and reduced expression of cyclin D1 and DNMT1 (18). On the other hand, there are conflicting data on the association between EGCG and sodium butyrate (NaB). It has also been shown that the association between these two substances, *in vitro*, induced cell cycle arrest in G1 phase in HT-29 cells and in G2/M phase in RKO and HCT-116 colorectal cancer cells. Furthermore, by combining the two substances in a dose of 10 μ M EGCG and 5 mM NaB, there was a reduction of cell proliferation using the RKO colorectal cancer cells (15).

CONCLUSION

Accumulating data show the potential protective effects of antioxidants in black tea, green tea and white tea, against IBD and colorectal carcinogenesis. The anticancer properties of tea flavonoids have been widely demonstrated *in vitro*, and their action favors cell cycle arrest, inducing apoptosis and interfering with the mechanisms responsible for tumor angiogenesis and distant metastasis. Moreover, tea flavonoids act on signaling pathways of the inflammatory processes, and this makes them good allies in IBD as they have the ability to modulate the inflammatory processes and reduce the associated symptoms. However, most studies are carried out on experimental animal models and

cell cultures and, therefore, we do not know the real effects on humans. It is desirable, therefore, to carry out studies on a human population or human-derived tissues in order to understand the real benefits of tea consumption on humans and consequently plan new therapeutic strategies.

REFERENCES

- Mazzola M, Carini F, Leone A, et al. Inflammatory bowel disease and colorectal cancer, nutraceutical aspects. *Euromed BiomedJ* 2016; 11(17):123-29.
- Tomasello G, Mazzola M, Leone A, et al. Nutrition, oxidative stress and intestinal dysbiosis: Influence of diet on gut microbiota in inflammatory bowel diseases. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2016; 160(4):461-66.
- Mazzola M, Carini C, Leone A, et al. IBD, malignancy and oral microbiota: analysis of literature. *Int J Clinical Dent* 2016; 9(4):273-78.
- Ukil A, Maity S, Das PK. Protection from experimental colitis by theaflavin-3,3'-digallate correlates with inhibition of IKK and NF- κ B activation. *Br J Pharmacol* 2006; 14(1):121-31.
- Kumar N, Shibata D, Helm J, Coppola D, Malafa M. Green tea polyphenols in the prevention of colon cancer. *Front Biosci* 2007; 12:2309-15.
- Hajiaghaalipour F, Kanthimathi MS, Sanusi J, Rajarajeswaran J. White tea (*Camellia sinensis*) inhibits proliferation of the colon cancer cell line, HT-29, activates caspases and protects DNA of normal cells against oxidative damage. *Food Chemistry* 2015; 169:401-10.
- Sreevalsan S, Safe S. Reactive oxygen species and colorectal cancer. *Curr Colorectal Cancer Rep* 2013; 9(4):350-57.
- Gardner EJ, Ruxton CH, Leeds AR. Black tea - helpful or harmful? A review of the evidence. *Eur J Clin Nutr* 2007; 61(1):3-18.
- Koňariková K, Ježovičová M, Keresteš J, Gbelcová H, Ďuračková Z, Žitňanová I. Anticancer effect of black tea extract in human cancer cell lines. *Springerplus* 2015; 4:127.
- Yang GY, Liao J, Kim K, Yurkow EJ, Yang CS. Inhibition of growth and induction of apoptosis in human cancer cell lines by tea polyphenols. *Carcinogenesis* 1998; 19(4):611-16.
- Fujiki H, Sueoka E, Watanabe T, Suganuma M. Primary cancer prevention by green tea, and tertiary cancer prevention by the combination of green tea catechins and anticancer compounds. *J Cancer Prev* 2015; 20(1):1-4.
- Jung YD, Kim MS, Shin BA, et al. EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. *Br J Cancer* 2001; 84(6):844-50.
- Cappello F, Conway de Macario E, Marino Gammazza A, et al. Hsp60 and human aging: Les liaisons dangereuses. *Front Biosci* 2013; 18:626-37.
- Moseley VR, Morris J, Knackstedt RW, Wargovich MJ. Green tea polyphenol epigallocatechin 3 gallate, contributes to the degradation of DNMT3A and HDAC3 in HCT 116 human colon cancer cells. *Anticancer Res* 2013; 33(12):5325-33.
- Saldanha SN, Kala R, Tollefsbol TO. Molecular mechanisms for inhibition of colon cancer cells by combined epigenetic-modulating epigallocatechin gallate and sodium butyrate. *Exp Cell Res* 2014; 324(1):40-53.
- Mazzon E, Muià C, Paola RD, et al. Green tea polyphenol extract attenuates colon injury induced by experimental colitis. *Free Radic Res* 2005; 39(9):1017-25.
- Hussein HI, Zgheib Z, Zeenny MN, Chams S, Assi TB, Chams N, Jurjus A. Epigallocatechin-3-gallate reduces mast cells activity TNF- α and NF κ B in colitis by interrupting an inflammatory cascade (MUC2P.827). *J Immunol* 2014; 192(S):68.11.
- Hu Y, McIntosh GH, Le Leu RK, Nyskohus LS, Woodman RJ, Young GP. Combination of selenium and green tea improves the efficacy of chemoprevention in a rat colorectal cancer model by modulating genetic and epigenetic biomarkers. *PLoS One* 2013; 8(5):e64362.