Polyphenol Supplementation as a Complementary Medicinal Approach to Treating Inflammatory Bowel Disease

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Polyphenol supplementation as a complementary medicinal approach to treating inflammatory bowel disease

Fiorella Biasi, Marco Astegiano[§], Marco Maina, Gabriella Leonarduzzi, Giuseppe Poli

Department of Clinical and Biological Sciences, University of Turin at San Luigi Gonzaga Hospital, 10043 Orbassano (Turin), Italy

[§]S.Giovanni Battista Hospital, Division of Gastroenterology, 10126 Turin, Italy

Corresponding Author:

Giuseppe Poli, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga Hospital, 10043 Orbassano, (Turin), Italy

phone: +39 011 6705422

fax: +39 011 6705424

e-mail address: giuseppe.poli@unito.it

Running title: intestinal inflammation and polyphenols

Abstract

Inflammatory bowel diseases (IBD) comprises a group of idiopathic chronic intestinal inflammation syndromes that are very common in developed countries. It is characterized by intermittent episodes of clinical remission and relapse, with recurrent inflammatory injury that can lead to structural damage of the intestine. The uncontrolled intestinal immune response to bacterial antigens leads to the production of abundant cytokines and chemokines, by activated leukocytes and epithelial cells, which trigger inflammatory and oxidative reactions. The current treatment of IBD consists in long-term anti-inflammatory therapy that, however, does not exclude relapses and side effects, frequently resulting in surgical intervention.

Polyphenols have been acknowledged to be anti-oxidant and anti-inflammatory and, therefore, have been proposed as an alternative natural approach, to prevent or treat chronic inflammatory diseases. Most studies have been in animal models of colitis, using chemical inducers or mice defective in anti-inflammatory mediators, and in intestinal cell lines treated with pro-inflammatory cytokines or lipid oxidation products.

These studies provide evidence that polyphenols can effectively modulate intestinal inflammation. They exert their effects by modulating cell signaling pathways, mainly activated in response to oxidative and inflammatory stimuli, and NF-kB is the principal downstream effector. Polyphenols may thus be considered able to prevent or delay the progression of IBD, especially because they reach higher concentrations in the gut than in other tissues. However, knowledge of the use of polyphenols in managing human IBD is still scanty, and further clinical studies should afford more solid evidence of their beneficial effects.

Key words: Chron's disease; flavonoids; gut; lignans; phenolic acids; stilbenes; ulcerative colitis.

INTRODUCTION

Inflammatory bowel diseases (IBD), is characterized by recurrent inflammatory injury and repair with consequent gross structural damage to the intestine. The etiology and pathogenesis of IBD are related to the complex interactions among environmental, genetic, cellular, and molecular factors, but it is still not clear how these components act and work together to trigger disease.

Genome-wide association studies have established a strong genetic component, which is likely to play a more prominent role in Crohn's disease than in ulcerative colitis (the most common IBD), although the loci identified to date are still limited, and their association with the disease accounts for less than 25% of cases [1].

In regard to the molecular events involved in these diseases, a defective immune system likely involves an altered immune response to some environmental agents and an abnormal response to commensal microbiota, which can lead to excessive production of pro-inflammatory cytokines with consistent intestinal mucosal injury causing erosion, ulceration, and strictures.

Besides cytokine production, another consistent feature of chronic intestinal inflammation is overproduction of different reactive oxygen species by activated leukocytes, which overwhelm the tissue's antioxidant defenses and most likely contribute to the functional impairment of the enteric mucosa [2,3].

It must also be taken into account that the intestinal tract is often exposed to oxidized foods, in particular lipids and their oxidation products, such as cholesterol and oxysterols, which might exert various alterations to the gut barrier's integrity, by perpetuating cell damage and contributing to IBD pathogenesis.

It has been proven that, in the intestinal mucosa of patients affected by Crohn's disease, the concentration of the most important antioxidants is markedly lower than in healthy subjects [4]. Prior to that, similar results had been obtained in rat experimental models of ulcerative colitis [5]. Recently, a genetic polymorphism of glutathione-s-transferase has been considered to be a possible cause of ulcerative colitis in different populations. Very interestingly, these polymorphisms have been associated with the development of cancer in ulcerative colitis patients [6, 7]: IBD is recognized to be a kind of pre-neoplastic disorder of the gut, and it has been proven that inflammatory and oxidative reactions are responsible for the increased risk of cancer development in these subjects [8].

The current IBD therapy, which mainly consists of the long-term administration of anti-inflammatory drugs, does not prevent intestinal fibrosis and stricture formation. Surgical intervention is necessary if pharmacological treatments is not successful, or in the case of complications such as fistulae, stenosis, or abscesses (particularly in Crohn patients). However, the reduction of pro-inflammatory cytokines in the plasma represents a logical target for IBD therapy.

Evidence gathered over the last decade suggests the possible health benefit of polyphenols. These compounds are widely distributed in all foods of plant origin, and exert many biological activities. Most polyphenols possess antioxidant properties, acting directly as free-radical scavengers or indirectly by interfering with specific proteins of red-ox signaling pathways involved in different biological functions [9]. Because a variety of polyphenolic compounds are found in foods, often as a mixture, and due to the even larger number of metabolites, it is quite difficult to elucidate the biomolecular mechanisms involved in their beneficial effects. Moreover, it is extremely difficult to estimate the daily average intake of polyphenols, as it depends on individual metabolism, eating habits, the analytical method used, as well as on differences in vegetable growth depending on seasonal and geographic variations [10-12].

Recent studies suggest the benefit of a dietary intake of polyphenols not only for their antioxidant properties, but also for their anti-inflammatory function, since they act as modulators of inflammation-related genes, i.e. cyclooxygenase-2, inflammatory interleukins, red-ox dependent transcription factors [13-14]. For this reason, increasing interest has been shown in the effect of these compounds in counteracting the development of human inflammatory and degenerative diseases, included intestinal ones.

This review will focus on the clinical and molecular features of IBD development, and on the recent advances in knowledge of the properties of polyphenols relevant to the treatment of IBD.

EPIDEMIOLOGICAL AND CLINICAL ASPECTS OF INFLAMMATORY BOWEL DISEASE

IBD comprises a group of idiopathic chronic inflammatory intestinal conditions. Crohn's disease (CD) and ulcerative colitis (UC) represent the two main categories of IBD.

Despite all the advances in the understanding of IBD, its pathogenesis is not yet fully understood. Genetic susceptibility of the host, and environmental factors, play roles in causing an inappropriate inflammatory response to intestinal bacteria, which leads to gastrointestinal injury.

IBD affects approximately 1.4 million patients in the United States, and 2.4 million in Europe [15]. Despite the fact that the occurrence of IBD is higher in Western than in Eastern countries, a recent increase in the incidence and prevalence has been observed in Eastern Europe and Asia [16]. In general, the prevalence of IBD is higher in countries in northern latitudes, especially in industrialized areas and among higher socio-economic classes. One possible explanation is the "hygiene hypothesis", first proposed by Strachan in 1989, which suggests that people with higher socio-economic status are less exposed to infections during childhood, so they do not develop a sufficient immune repertoire, through not experiencing noxious organisms [17]. This theory may explain the increased occurrence of allergic and immune-mediated chronic diseases, including IBD [18-19]. However, other factors can influence the diagnosis of IBD, which, for example,

in the United States appears to be commoner in commercially-insured individuals than in those insured by managed programs (Medicaid) [20]. The peak age of incidence of CD is 30-40 years, with a decreased incidence with age, while the incidence rate of UC is quite stable between the third and seventh decades. Different studies suggest an increasing trend of incidence in childhood-onset IBD, but results differ, depending on populations and ethnic groups considered: Abramson and coworkers showed that the prevalence of UC was higher than that of CD in pediatric patients in Northern California [21]; on the contrary, data relating to the young French population indicate higher rates of pediatric CD than of UC [22].

The features which normally distinguish CD from UC are the presence of lesions proximal to the colon, perineal disease and fistulas in CD, whereas UC shows diffuse mucosal inflammation limited to the colon.

From the histological standpoint, CD is characterized by patchy transmural inflammation, with the presence of lesions along the whole tract of the mucosa, and of granulomas, whereas the inflammation in UC is confined to the superficial layers of the colonic mucosa. The number of CD patients showing granulomatous lesions or fistulas reach 50% and 25%, respectively [19]; granulomas are especially localized in the ileo-cecal, colic, or ileo-colic areas, but may affect any part of the gastrointestinal tract from the mouth to the anus; they are often associated with extra-intestinal complications.

IBD is typically considered to be a chronic intermittent disease. Most patients with IBD experience intermittent episodes of active disease, ranging from mild to severe during relapses, alternating with variable periods of remission, in which the illness may decrease in severity or disappear. Unfortunately, around 80% of those affected by Crohn's disease require surgery once in their lives. A high percentage (above 30%) relapse and require further surgery [15].

The individual course of UC is often unpredictable, but these patients show a high probability (67%) to relapse at least once during the ten years after diagnosis. A prospective study, on seven defined geographic areas plus Israel, showed that the risk of relapse increased in those aged below 30 at diagnosis; furthermore, multiple relapses for UC were more probable in those with a shorter time between diagnosis and first relapse [23].

Diagnosis of IBD requires a systematic approach, including a comprehensive symptomatological analysis, a full medical history of patient and family, accompanied by stool and blood tests, radiographic and endoscopic analyses, and biopsy for histological assessment. Fecal hemoglobin, α1-antitrypsin and neutrophil-derived proteins, including calprotectin and lactoferrin, are considered to be markers of active IBD. Hemoglobin and lactoferrin are particularly elevated in almost all UC patients, whereas α1-antitrypsin is particularly elevated in CD [24]. The main laboratory blood tests currently used to measure inflammation in clinical practice are C-reactive protein and erythrocyte sedimentation rate. These parameters, associated with endoscopic and histological evidence of acute inflammation, are useful for

diagnosis and can reflect the natural history of IBD, but are not predictors of relapse [25].The cytokines IL-1, IL-6 and TNFα appear to be emerging as acute-phase markers in the serum; however, testing for them is still too expensive for routine use [26]. Two serum antibodies, anti-*Saccharomyces cerevisiae* antibodies and perinuclear-staining anti-neutrophil cytoplasmic antibodies, are of great interest for differential diagnosis and management of IBD. These antibodies reflect the loss of tolerance toward bacterial and fungal flora [27].

In general, symptoms depend on the segment of the intestinal tract involved: patients with IBD may present stool containing mucus or blood, incontinence, tenesmus, abdominal cramps and pain.

Perpetuation of the inflammatory processes, which involve all layers of the intestinal tissue, i.e. mucosa, muscularis mucosa, submucosa and sierosa, leads to fibrosis and eventually strictures that induce intestinal obstruction, a commonest local complication in CD. Bowel perforation and consequent intra-abdominal fistulas and abscesses are characteristic of CD patients. UC patients are more likely to develop extensive colitis or pancolitis, with megacolon and colon carcinoma. Extra-intestinal complications, including peripheral arthritis and hepatobiliary diseases, affect more than 25% of IBD patients [for a comprehensive review see 28].

IBD management often entails long-term treatment with classical anti-inflammatory agents, such as aminosalicylates, and corticosteroids. Recently, immunomodulators, (thiopurines, cyclosporin A and methotrexate) or anti-TNFα antibodies (infliximab, adalimumab, and certolizumab) are accepted in the treatment of patients with inadequate response to the standard treatment with aminosalicylates and steroids. However, all bring a risk of important side effects, including the reactivation of latent tuberculosis and of hepatitis B. Table 1 describes the main drugs used in IBD management; they are taken from the guidelines developed in the year 2010 by the World Gastroenterology Organization for the diagnosis and management of IBD [19]. IBD patients, thus, often require extensive surgical resection of the gastrointestinal tract, which severely impairs intestinal absorption and metabolic function, depending on the extent of the resected bowel.

Table **1**. Therapeutic approaches for IBD.

Aminosalicylates	Corticosteroids	Immune modifiers	Anti-TNFα agent	Antibiotics (in CD)
Sulfasalazine	Orally:	Thiopurines:	Infliximab	Metronidazole
Mesalazine	- Prednisone	- 6-mercaptopurine	Adalimumab	Ciprofloxacin
Olsalazine	- Prednisolone	-azathioprine	Certolizumab	
Balsalazide	- Budesonide,	Calcineurin inhibitors:		
	- Dexamethasone	-cyclosporin A (in UC)		
	Intravenously:	- tacrolimus (in CD)		
	- Hydrocortisone	Methotrexate		
	- Methylprednisolone			

According to the World Gastroenterology Organization Practice Guidelines in the year 2010 [see 19].

CELLULAR AND MOLECULAR ASPECTS OF INFLAMMATORY BOWEL DISEASE

The gastrointestinal tract is responsible for host defenses against pathogens and for immune tolerance toward commensal microbiota. The chronic inflammation in IBD is characterized by a dysregulation among innate, adaptative, and tolerogenic immune responses, which results in massive gut infiltration by granulocytes and macrophages. These cells produce large amounts of pro-inflammatory cytokines, chemokines and reactive oxygen intermediates, which amplify inflammation and cause extensive damage to the mucosa.

An unbalanced ratio between oxidative reactions and antioxidant defenses, leading to the disruption of intestinal cell membranes, has been demonstrated in IBD patients [29,3]. Furthermore, ROS and their oxidative end-products are now considered to be second messengers, able to activate different signal transcriptional factors, in particular NF-κB. These signals, exacerbate the pro-inflammatory and pro-apoptotic events, leading to cancer development [30].

Since hyper-responsiveness of the host mucosa against intestinal flora plays an important role in inducing inflammation, it is important to focus attention on the role played by intestinal epithelium in IBD. In the intestinal tract, numerous cell types serve the common function of maintaining a correct immune response. These comprise, firstly, the epithelial barrier and the gut associated lymphoid tissue, which essentially comprises Peyer's patches, lamina propria lymphoid tissue, and intraepithelial lymphocytes.

Cells involved in inflammatory response

Epithelial cells normally secrete mucus, which acts as a physical barrier preventing attachment of luminal antigens; in addition, these cells actively participate in presenting antigens and secreting a large number of pro- and anti-inflammatory cytokines. Of the different cytokines, considerable attention has been paid to TNFα activity in the pathogenesis of IBD, because of its pro-inflammatory and pro-apoptotic effect: TNFα blockers have become a mainstay in IBD therapy [31].

Defects in the mucosal barrier may be involved in the pathogenesis of IBD, the overt inflammatory response possibly being due to excessive permeability to infections. Increased intestinal paracellular permeability has been found in an *in vitro* model of colitis, in epithelial-specific IκBα mutant transgenic mice [32], as well as in another experimental model of IBD, in which rat colon was exposed to TNFα and IFNγ [33]. Impaired expression of human endogenous antimicrobial peptides by epithelial cells, for example α-defensin 2, has been associated with increased susceptibility to colonic mucosa in CD [34].

Mucosal activated CD4+Th lymphocytes are responsible for maintaining chronic inflammation. After stimulation of naïve CD4+ Th cells, lymphocytes proliferate and differentiate into different subsets, namely Th1 and Th2 cells, which produce different cytokines. Th1 cells, the main mediators of Type1 immunity, are characterized by intense phagocyte activity, and mediate immunity against intracellular pathogens, producing IL-2, IFNγ, and TNFα; these, in turn, induce TNFα, IL-6, and IL-1ß release from macrophages. Th2 cells mainly synthesize IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25, and are required for the generation of proper classes of antibodies, and the elimination of extracellular pathogens [35]. Another subset of T lymphocytes, with a function distinct from those of Th1 and Th2, is the Th17 subset, which secretes IL-17, and seems to play a role in host defense against extracellular pathogens, by recruiting neutrophils and macrophages when Th1-type and Th2-type immunity fails to clear them [36]. Th17 cells require IL-23 for their differentiation and function. IL-23 orchestrates different pro-inflammatory pathways, both dependently and independently, by Th1 and Th17 cells [37].

Th1 and Th17 cell-related cytokines, i.e. TNFα, IFNγ, IL-12, and IL-17A, IL-21, IL-23, are selectively activated in active CD, while Th2-related cytokines, such as IL-5 and IL-13, are increased in the inflamed mucosa of UC. IL-1, secreted by natural killers, is directly involved in the cytotoxic effect of the intestinal epithelium, which can be partially responsible for the mucosal ulceration in UC [38, 39]. Patients with late active CD showed higher tissue and blood levels of IL-17 than those with early disease [40]. However, controversial studies indicate significant IL-17 mRNA up-regulation in CD4+ cells isolated from the mucosal lamina propria of UC patients, as well as increased IL-23 receptors, in

both UC and CD, with enhanced IFNγ only in CD, indicating that IL-23 and IL-17 may also be involved in UC pathogenesis [41].

Regulatory T (Tregs) lymphocytes are another specific subset of T cells, showing a CD4+CD25(high) phenotype in humans, and are characterized by expression of the transcription factor FOXP3. Tregs are induced by two cytokines with high anti-inflammatory effect, IL-10 and TGFβ1. Functional Tregs play an essential role in controlling the host-microbe interaction in the gut, because of their immune-regulatory properties, since they inhibit activation of Th1 cells against enteric bacterial antigens [42]. An example of this is that Tregs are able to regulate Th1 cell response, by controlling the Th1-specifying transcription factor T-bet; IFNγ also plays a key role in the induction of T-bet expression by Tregs [43]. It has been shown that CD4+CD25+ Tregs prevent and resolve intestinal inflammation, in a murine T cell transfer model of colitis [44]. Patients with UC or CD showed a decreased number of peripheral suppressive FOXP3+CD4+ Tregs during active disease phases. However, the study found an expansion of the FOXP3+CD4+ Treg cell population in mucosal lymphoid tissues [45, 46], supporting the hypothesis that Tregs move to sites of inflammation, in an attempt to restore immune homeostasis.
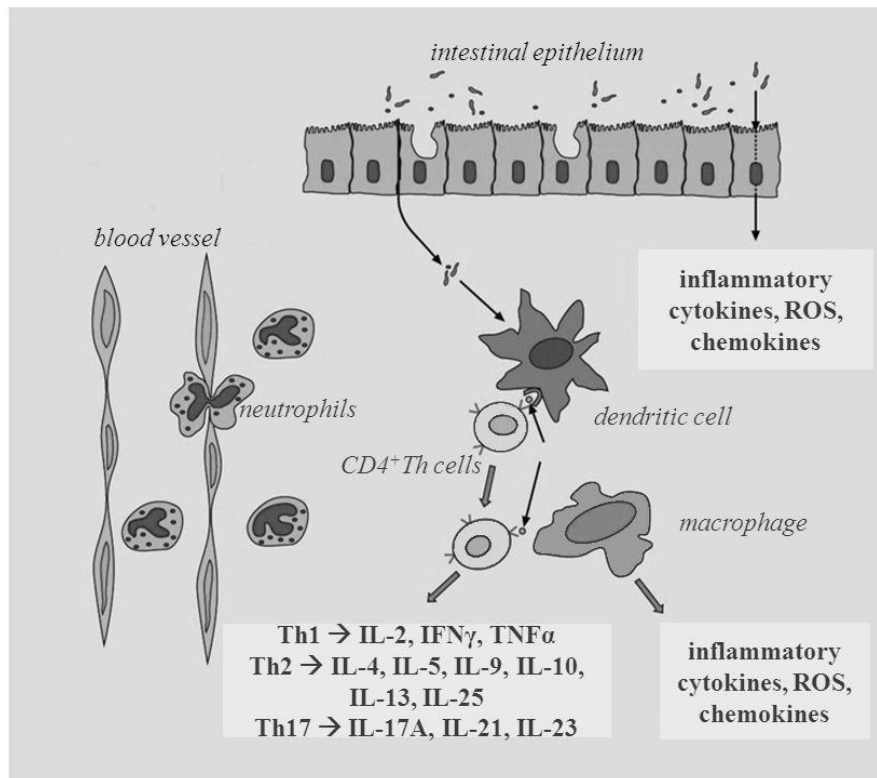
Figure **1**. Pathogenesis of inflammatory bowel disease.

Commensal bacteria in the lumen may induce an acquired immune response by the bowel mucosa, reacting with dendritic cells either directly or through the induction of the production of inflammatory cytokines, chemokines and ROS in the mucosa's epithelial cells.

Activation of classic antigen-presenting cells, such as dendritic cells, promotes the differentiation of type 1 T helper lymphocytes (Th1) and type 2 T helper lymphocytes (Th2) that produce distinct profiles of cytokines. Th1 cell-related cytokines are selectively activated in active CD patients, while cytokines secreted by Th2 cells are increased in inflamed mucosa of UC patients.

Another subset of T helper lymphocytes (Th17), which can be induced by dendritic cells and differentiate along a pathway distinct from those that give Th1 and Th2 subsets, is important in IBD pathogenesis. The synthesis of Th17 cell-related IL-17A, IL-21, IL-23 appear to be more increased in CD than in UC.

Cytokines involved in inflammatory response in the gut

The interplay between activated immune cells, epithelial cells, and mesenchymal cells, in managing the intestinal inflammatory response is essentially mediated by complex cross-reactions among cytokines and chemokines (Figure 1).

Clinical attempts employing TNFα blockers clearly indicate that cytokines are the therapeutic targets in IBD patients. The effect of TNFα as inducer of apoptosis in activated inflammatory cells is widely known. The use of Infliximab, a monoclonal anti-TNFα antibody, is widely accepted in the treatment of acute and subacute CD; in patients with moderate to severe CD who are resistant to conventional steroid treatment, repeated infusions of Infliximab can maintain remission for up to 44 weeks [47].

Expressions of the IL-1β, IL-6 and TNFα are increased in affected mucosa from patients with active IBD, while IL-2 and IFNγ are down-regulated in peripheral blood cells [26]. A direct correlation between IL-6 serum levels and disease severity has been found in both pediatric UC and CD [48]. More recently, Umehara and colleagues have confirmed that serum IL-6 levels are correlated with clinical activity, and that, upon anti-inflammatory therapy, the decrease of IL-6 is directly correlated with reduction of disease activity [49]. IL-6 and IL-23 synergize to promote Th17 generation. In Il-10 deficient mice spontaneously developing enterocolitis, and in a T cell-transfer model of colitis, Yen and coworkers found that IL-23-activated Th17 cells produced large amounts of IL-17 and IL-6, suggesting a synergistic action of these two cytokines in the inflammation [50]. Recent discoveries stress the major role of IL-17 and IL-23 in the development of chronic intestinal inflammation: in IBD excess IL-23 is essential to promote development and expansion of a pathogenic IL-6/IL-17–producing memory-activated T cell population [51]. Conversely, IL-23 shares a common p40 promotor in dendritic cells with IL-12, which is highly expressed in CD [52]. In addition, levels of Th17-producing IL-17 and of IFNγ are higher in CD than in normal gut mucosa, and treating intestinal lymphocytes with IL-23 enhances, respectively, IL-17A and IFNγ, in UC and CD, suggesting that IL-23 differentially regulates the Th1/Th17 balance in IBD [41].

TGFβ1 and IL-10, chiefly maintain gut homeostasis, down-regulating both the immune response and the pro-inflammatory mediators implicated in innate and adaptative immune responses. FOXP3+CD4+ Tregs can be activated through IL-10- and/or TGFβ1-dependent mechanisms. A deficit in these two cytokines might also be involved in the development of IBD. Experimental models of mice with targeted deletion of the IL-10 gene, spontaneously developed chronic enterocolitis [50, 53]. IL-10 has been found to reduce the antigen-presenting capacity of monocytes and dendritic cells [54]. Impairment of IL-10 signaling has been reported in a pediatric group of IBD patients with granuloma-positive colitis [55]. TGFβ1 knockout mice have been generated, but they developed extended multi-organ autoimmunity [56]. TGFβ1 has a predominantly anti-inflammatory effect on CD4$^+$ T cells in the absence of IL-23; lymphocytes isolated from

transgenic mice with a dominant-negative form of TGFβ1 receptor II induced a significant colitis when they were transferred to IL-23-deficient RAG mice [57]. In a Th1-dependent experimental colitis model, TGFβ1 induced the expression of a specific peripheral FOXP3 CD4+CD25+Treg population with immune suppressive capacity [58]. Even if the properties of TGFβ1 are predominantly anti-inflammatory, this cytokine must be considered as a regulator of the balance between anti- and pro-inflammatory events. Naïve T cells stimulated with TGFβ1 and IL-6 secreted large amounts of IL-17, whereas IL-23 might triggered the proliferation of Th17 cells. TGFβ1 thus, acts in Th17 cell development to confer IL-23 responsiveness [59].

The role of NF-κB in the intestinal inflammation

The red-ox sensitive transcription factor NF-κB plays a central role in regulating the immune response associated with inflammatory reactions in IBD. This transcription factor is classically activated by a large number of stimuli, including cytokines, microbial products and oxidative stress. In mammals, NF-κB consists of five members, namely p65/RelA, c-Rel and RelB and the p50 and p52 proteins, which are produced by proteolysis of the p105 and p100 precursors, respectively. NF-κB dimers are normally in the inactive state because of their association with their inhibitors, IκBα, IκBβ, IκBε, p100 and p105. Upon cell stimulation, a IκB kinase phosphorylates IκB proteins on specific serine residues, inducing their ubiquitination and proteosomal degradation. NF-κB dimers thus become free to accumulate in the nucleus and to activate gene transcription. IκB kinase consists of two subunits, IKK1 (or IKKα) and IKK2 (or IKKβ), plus the regulatory subunit named NEMO.

Multiple evidence suggests that NF-κB activation actively contributes to the development and maintenance of intestinal inflammation. This transcription factor has a dual function in the regulation of gut homeostasis: it provides epithelial and immune cells with the capacity to protect gut from pathogen agents, and NF-κB hyper-activation contributes to amplifying intestinal inflammation.

Microbial recognition of intestinal bacteria by intestinal epithelial cells involves the activity of a pattern of recognition receptors, TLRs, NOD and NLRs. TLRs, upon recognition of bacteria-derived lipopolysaccharide, flagellin or unmethylated CpG, recruit the adaptor proteins MYD88 and TRIF, which subsequently activate NF-κB. NODs (NOD1 and NOD 2) recognize bacteria-derived peptoglycan and activate NF-κB recruiting the receptor-interacting protein 2 (RIP2). Commensal bacteria can regulate the levels of NF-κB , whereas pathogenic bacteria induce TLR- and NLR-mediated NF-κB activation [60]. It has been shown that MyD88 deficiency prevents colitis development in IL-10$^{-/-}$ mice [61]. Genetic factors, especially the pattern-recognition receptor *NOD*2 gene mutation, the major accepted genetic polymorphism in CD, induce potent NF-κB activation, leading to compromised host defense and mucosal damage [62].

Therefore, disruption of the epithelial layer with the malfunctioning of microbial ligands, might result in the loss of tolerance to commensal bacteria, with the up-regulation of NF-κB in a pro-inflammatory sense.

High levels of NF-κB have been found in the mucosal cells of IBD patients [63]. Administration of the NEMO-binding domain peptide inhibited IKK activation and reduced the severity of colon inflammation, in mouse models of colitis. A decreased expression of mouse β-defensine 3 was detected in NEMO-deficient intestinal cells, which displayed the abrogation of NF-κB activation, resulting in impairment of mucosal integrity and of gut's antimicrobial defenses, with a rise in chronic intestinal inflammation [64].

Therefore, proper regulation of NF-κB activity at the intestinal epithelial site is important for the correct activation of immune and inflammatory responses to microbial attack, suggesting that strategies targeting NF-κB have a great potential in therapeutic strategies in IBD.

POLYPHENOLS AND INTESTINAL INFLAMMATION

Polyphenols are a heterogeneous group of plant secondary metabolites, which are introduced into humans with the diet. These compounds generally contribute to plant defenses against environmental insult. Polyphenols function as colorants, flavorings and antioxidants, improving food quality.

Extensive literature on the protective effect of polyphenols against diseases characterized by oxidative stress and inflammation, such as cardiovascular and degenerative diseases and cancer, is now emerging [9, 65-67].

The main classes of polyphenols are flavonoids, phenolic acids, lignans and stilbenes; chemically, they are characterized by the presence of differing numbers of phenolic rings, with two or more hydroxyl groups (see Figure 2). These structures are hydrogen or electron donors, acting as scavengers of free radicals. There are more than 5000 flavonoids; they contain two aromatic rings linked by three carbons, which originate an oxygenated heterocycle [68]. Based on the degree of unsaturation and oxidation of their heterocycle, flavonoids are divided into several subclasses: flavones, isoflavones, flavonols, flavanols, flavanones, anthocyanins and anthocyanidins.
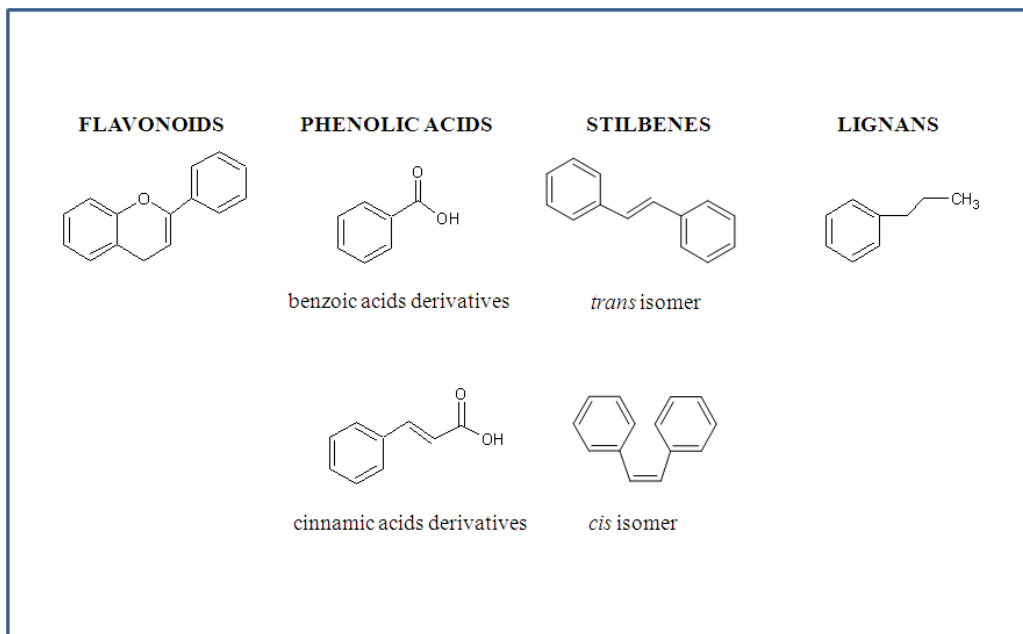
Figure **2**. Chemical structures of the main classes of polyphenols.

The degree of oxidation, the presence of substitutions and/or polymerization of the basic structure of polyphenols characterize the different flavonoid, phenolic acid, stilbene and lignan derivatives.

The beneficial effects of polyphenols depend on various factors: dietary habits, food processing methods, absorption, metabolism, derived compounds and their potential bioactivity. The average daily intake in Western populations is approximately of 1g/day [69].

During food storage and handling, some components rich in phenolic compounds can be lost. High temperatures during food processing are the main factor responsible for modifications of phytochemicals in general. Boiled onions and tomatoes lose up to 80% of their flavonoid quercetin content [70]; this quercetin may also be lost in peeled fruits [71]. During refining of wheat, many polyphenols, present in the outer layer of the grain, are lost [72].

Bioavailability of polyphenols is generally not very high, because they are poorly absorbed and rapidly catabolized. Maintenance of their high concentration in blood and tissues thus requires repeated ingestion of significant amounts of polyphenols over time.

Generally these compounds are ingested in conjugated form: certain classes of flavonoids are glycosylated with different sugars, such as glucose or rhamnose, while others are acetylated or esterified. The first step of metabolism occurs in the small intestine, where β-glycosydase activity mainly occurs in the mucosal enterocytes during polyphenol transfer from the apical to the basal side of the cells, or, in some cases, is dependent on enteric bacteria. Because they

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express glycosidase, human cells are able to cleave glucose, arabinose and xylose. On the contrary, humans have no rhamnosidases, meaning that rhamnose can only be cleaved by colonic microflora. The deconjugated aglycone form must be reconjugated by glucuronydation, methylation or sulfation. This step requires specific transferases (i.e glucuronyl-transferase, phenol-sulfo-transferase, acetyl-transferase) and takes place in the intestine when doses of polyphenols are low. On the contrary, when higher doses are ingested, the conjugation takes place predominantly in the liver. Polyphenols that, cannot be absorbed in the small intestine, such as phenolic acids, and those that are metabolized in the liver and transported back into the lumen of the large intestine through the bile, reach the colon. Here, colonic bacteria are extremely important, because they have large amounts of catalytic and hydrolytic enzymes able to break polyphenols down into simpler compounds [69]. This implies that the gut, with its microbiota, is closely involved in the metabolism of polyphenols, which reach higher concentrations in this organ than elsewhere.

Most clinical studies on polyphenols examine the possibility of reducing the risk of developing different cardiovascular diseases, such as atherosclerosis, obesity and insulin resistance, myocardial infarction, and preventing cancer [73]. For instance, six prospective cohort studies in humans evidenced that flavonol intake was inversely associated with nonfatal and fatal stroke [74]. Isoflavones, genistein and daidzein, lignans and coumestans, have been shown to relieve cardiovascular complications and prevent osteoporosis in menopausal women [75]. A strong inverse association between green tea flavanol consumption and coronary artery disease has been found in a large cohort of Japanese patients who underwent coronary angiography [76]. Flavanols are believed to diminish cardiovascular risk factors, reducing total blood cholesterol and suppressing the production of oxidized LDL deposited in atherosclerotic plaques; they also reduce platelet adhesion, related to thrombotic events [77]. Flavanols were found to improve endothelial functions and reduce the concentration of peripheral blood inflammatory biomarkers, both in patients with metabolic syndrome [78], and in those with rheumatoid arthritis [79] and cerebral ischemia/reperfusion injury [80]. A double-blind randomized crossover study to placebo versus antocyanins suggests the potential anti-hypertensive function of these substances [81]. Recently, clinical study has shown that resveratrol might improve insulin sensitivity in Type-2 diabetic patients, lowering oxidative reactions, and consequently regulating PI3K/Akt cell survival pathway related to insulin signaling [82].

Widespread reports have suggested that the beneficial role of polyphenols for human health comes from something other than a simple antioxidant effect. A new concept of the biological activity of these compounds has received much attention: they interact with specific signaling proteins, which mediate gene regulation in response to oxidative stress and inflammation [for a review see 83]. Numerous signals appear to be regulated by these compounds

(MEK, ERK, p38 MAPK, PI-3K/Akt, STAT-1). Among the different signaling pathways, the down-stream transcriptional factor mainly involved in the cellular regulation mediated by polyphenols appears to be NF-κB.

Few clinical trials have studied the effects of polyphenols in intestinal diseases; most have been performed on experimental colitis animal models and on intestinal cell lines.

It will now be attempted to summarize the available literature pertaining to the biological effect of polyphenols, in regard to protection against intestinal inflammation, focusing on the critical cell pathways regulated by these compounds.

FLAVONOIDS

Flavones

Luteolin and apigenin are members of the group of flavones: they are present in different vegetable, such as sweet red pepper and onions (luteolin), parsley and celery (apigenin), as well as in flowers.

Their bioavailability is very low compared to other flavonoids. They are usually glycosilated in food, but their conversion into their derived metabolites appears also to be mediated by commensal microbes, i.e. *Clostridium orbiscindens* and *Enterococcus ramulus* [84].

The role of these flavones is not fully understood: various different beneficial effects of these compounds as potential anti-inflammatory compounds have been suggested. Their main role in cell signaling appears to be that of inhibiting pro-inflammatory mediators by inhibiting NF-κB activation [85, 86]. They can be considered anti-tumor agents, because they are able to reduce HIF-1α and VEGF-induced angiogenesis [87, 88].

There are few data about their effect on intestinal damage. One of the most representative studies was on an *in vitro* model of inflammation in murine non-carcinoma intestinal epithelial cells Mode-K, which were stimulated by TNFα and IL-1ß. Apigenin, luteolin, and 3'-hydroxy-flavone inhibited gene expression of the T cell chemoattractant IP-10, specifically activated by TNFα. The three compounds appeared to interfere with induction of Akt-dependent survival signaling, via NF-κB pathway. However, these flavones appeared to act differently from on another at different sites of the NF-κB and Akt cascades, with the same downstream IP-10 target. Furthermore, luteolin and 3'-hydroxy-flavone selectively induced degradation of the interferon regulatory factor IRF-1, which is normally enhanced and stabilized during inflammation activated by TNFα [89]. Other studies on both the intestinal cell line HT29 treated with TNF-α, and on IL10^{-/-};NF-κB ^{EGPF} transgenic mice, which express the reporter gene EGFP under control of the NF-kB promoter, report contrasting results. In the mouse model, acute colitis was induced by giving the animals 3% DSS in their drinking water for 6 days; one group was pre-fed with a diet containing luteolin. These mice developed intense acute inflammation

of the mucosa, with necrosis which progressed toward fibrosis and granulomatosis. DSS-induced colitis was partially triggered by an aberrant or exaggerated immune responses to bacterial antigens derived from the intestinal lumen. In contrast with the findings of other studies, luteolin-fed mice exposed to DSS showed exacerbated colitis, probably because the apoptotic cascade had been activated. In addition, the study found that luteolin sensitized HT29 cells treated with TNFα to induce caspase-3 activation and DNA fragmentation. These effects were associated with blockage of NF-kB signaling induced by TNFα, stressing that enhancement of NF-kB must also be considered as a protective whereby enterocytes counteract the increased uptake of luminal bacteria during a mucosal damage. Use of these polyphenols should be controlled, since ingestion of herbal compounds often occurs without medical supervision [90].

Isoflavones

The most widespread isoflavones are genistein and daidzein, which are found in soy and other *Leguminosae*. They are considered to be the best-absorbed flavonoids, although they are not the major components of the Western diet.

Genistein and daidzein are normally introduced into the diet as glycosides, and are subsequently rapidly absorbed in the gut as aglycones; absorption mainly occurs in the upper gastrointestinal tract [11]. This has been confirmed by a study on subjects with ileostomy, versus healthy subjects fed isoflavone glycosides: the ileostomy patients appeared to absorb aglycones with a comparable degree of efficiency to the healthy subjects [91].

In only 35% of the population dadzein is rapidly converted to equol by the luminal intestinal bacteria. Inter-individual variation in the conversion of daidzein to equol has been attributed to differences in the gut microflora composition, and may partly explain the contrasting results on equol administration reported by different clinical studies [92].

These compounds have mainly estrogenic properties, and thus far have been studied as an adjuvant endocrine therapy in human breast cancer, and as preventive compounds in the development of hormone-sensitive cancers, being competitive antagonists of estrogen receptors (ER) [93, 94]. Unfortunately, other and contradictory results show that these isoflavones can also exert genotoxic effects, because of their hormonal activity [95].

In experimental models, administration of genistein to the differentiated human colon CaCo2 cell line, exposed to conditions mimicking *in vivo* inflammatory situation, has been reported to lower important cytokines that are involved in intestinal inflammation processes. The cells were differentiated into enterocyte-like cells with absorbent properties, and treated with a cocktail of cytokines (IL-1β, TNFα, IFγ) and LPS. Incubation of CaCo-2 cells with genistein halved the IL-6 and MCP-1 overproduction. In this same experiment, another kind of flavonoid, epigallocatechin-3-gallate, was also able to decrease IL-6 and IL-8, by 60% and 50% respectively [96]. However, another *in vitro* intestinal model of Mode K

cells induced with TNFα, showed that genistein did not decrease expression of IL-6, and even increased IL-1ß [89]. Human colon adenocarcinoma DLD-1 cells, with or without ER-β gene silencing by RNA interference, were exposed to a mixture of soy isoflavones, comprising genistein, daidzein, and glycitein. Cell-cycle arrest occurred in the cells treated with isoflavones, associated with up-regulation of cyclin dependent kinase inhibitor p21. These events were not observed in the ER-β gene silenced cells. Furthermore, ERK-1/2 and Akt expressions were unaltered, and NF-κB was modestly up-regulated, by soy isoflavones [97].

These contrasting results suggest that these phenolic compounds possess different and sometimes conflicting actions.

Favonols

The most widespread flavonols are quercetin, myricetin and kaempferol. Quercetin is particularly abundant in our diet, being present in onions, apple peel, tea, and tomato juice.

They are usually present in foods in the glycosylated form. The most widely-studied flavonol is quercetin, the predominant form being quercetin-β-glycoside. Quercetin-3-O-rhamnoglucoside (rutin) and quercetin-3-O-rhamnoside (quercitrin) also exist, and can be hydrolyzed to quercetin only by the gut microflora in the large intestine, because human cells do not express rhamnosidases [69].

These compounds are marketed either as dietary supplements or as pure compounds, and have been investigated in depth. Most studies have been performed *in vitro* or on animal models. Quercetin and kaempferol have been found to suppress allergic inflammation in intestinal epithelial CaCo-2 cells, mimicking allergy after stimulation with IL-4 or immunoglobulin (Ig) E-allergen. Regulation of p38 MAPK activity appeared to be the major transduction pathway involved in the IgE-mediated allergic inflammation that was suppressed by these two flavonols [98]. Quercetin blocked activation of STAT-1 and NF-κB, in RAW 264.7 macrophages stimulated by gliadin in association with IFNγ, suggesting this compound could represent a possible natural approach to controlling intestinal inflammation in celiac disease [99].

In epithelial tight junctions of CaCo-2 cells, whose function is to maintain paracellular permeability in the intestinal mucosa, quercetin enhanced the expression of the tight junction protein claudin-4, which increased paracellular permeability, improving intestinal barrier function [100]. However, different chemical structures of these compounds can be absorbed differently, and may exert different biological effects. The secretion of T84 colonic epithelial cells is potently stimulated by quercetin, but not by rutin, nor myricetin. Some effects of flavonols may be affected by glycoside modifications: some enzymatic activities and protein expression in Caco-2 cells differ among quercetin, quercetin-glucoside, and quercetin-rutinoside [101, 102].

Experimental colitis was induced in female Wistar rats by treatment with TNBS; the rats then showed diffuse hemorrhagic necrosis of the mucosa, and bowel-wall thickening along the colon. In this animal model, 3-rhamnosyl-quercetin (quercitrin) had no effect on levels of neutrophil myeloperoxidase, but decreased alkaline phosphatase, and prevented increases of both the oxidative stress end-product malonaldehyde, and nitric oxides. This improvement was associated with amelioration of a permeability defect due to the disordered hydro-electrolytic transport that occurs in inflamed mucosa. Interestingly, treatment with quercitrin exerted a slight but significant increase in absorptive capacity, and also normalized secretion, especially in the proximal colon, but only at high doses (5 mg/kg) [103]. It must taken into account that flavonols are in part transformed by intestinal anaerobic bacteria, and thus the concentration of quercetin absorbed by the epithelial cells could be lower than ingested.

In another experimental model of rat colitis, induced in female Wistar rats watered with DSS, quercitrin exerted intestinal anti-inflammatory effects and improved the oxidative status of the colonic mucosa. This improvement appeared to be mainly dependent on reduction of the inducible form of nitric oxide synthase (iNOS) expression, associated with a significant down-regulation of colonic NF-κB [104].

Quercetin has also been shown to inhibit expression of the pro-inflammatory cytokines, IP-10 and MIP-2, in primary intestinal epithelial cells isolated from TNFΔARE/WT mice fed with the flavonol. TNFΔARE/WT mice develop experimental ileitis because they lack the translational repression of TNFα. Quercetin inhibited IP-10 and MIP-2, hampering the NF-κB binding to the cytokine gene promoters [105].

Flavanols

Flavanols are catechins that are very abundant in green tea (*Camelia Sinensis*). The beneficial properties of green tea have been known for centuries in Eastern cultures, and are related to its high catechin content. It contains (-)epigallocatechin-3-gallate (EGCG), (-)epigallocatechin, and (-)epicatechin, which have very strong reducing power. Among the catechins contained in green tea, that with the strongest biological activity is EGCG.

Bioavailability of flavanols is high; they are almost always present in the diet in the non-glycosylated form, so unlike other flavonoids they do not require the action of β-glycosidase. They are mainly absorbed in the small intestine; however, absorption is low, because they rapidly bind to luminal proteins acting as bactericides [106].

The impact of dietary flavonoids in the development of colorectal cancer was analyzed statistically in a large-scale Netherlands Cohort Study: among the flavonols, flavones and catechins analyzed, an association was found between total catechin intake, (+)-catechin intake and (-)-epicatechin intake and decreased risk of rectal cancer in overweight men.

An inverse correlation was also found between flavanol and flavonol intake and colon cancer in normal-weight women. However, as the study authors point out, these data do not fully agree with those of the other clinical studies [107].

It has recently been suggested that EGCG might target the Met receptor tyrosine kinase, which is principally involved in cancer development. In HCT116 human colon cancer cells, this flavanol was found to inhibit phosphorylation of the c-Met receptor and activation of its downstream proteins AKT and ERK, both involved in tumor development and in inflammatory processes [108].

In intestinal cancer HT29 cells, EGCG was found to induce apoptosis and reduce the phosphorylated forms of ERK and Akt, which are implicated in proliferative and survival cell signaling [109]. EGCG was found to down-regulate AP-1 signaling in fibrotic transfected hepatic stellate cells [110]; the compound also blocked TNFα-induced IKK and NF-κB activity in the IEC-6 intestinal epithelial cell line [111]. Other studies on different tissues have confirmed these mechanisms: for example, EGCG markedly attenuated severe ischemia/reperfusion injury induced in rat liver, by lowering oxidative stress, down-regulating NF-κB and c-Jun signal transduction pathways, and preventing tissue damage from both necrosis and apoptosis [112]. EGCG pretreatment of CaCo-2 cells, in which inflammation was induced by TNFα, inhibited IκBα degradation in a dose-dependent manner. Furthermore, EGCG inhibited AKT phosphorylation, an upstream step necessary for IκBα degradation and NF-κB activation. This latter study demonstrated that the inhibitory effect of EGCG on TNFα-induced NF-κB activation was mediated by the release of adenosine; thus, this compound might have not only anti-inflammatory action, but also anti-cancer properties [113].

Our own recent studies on differentiated intestinal CaCo-2 cells show that a mixture of oxidized cholesterol compounds, i.e. oxysterols, which are representative of a hyper-cholesterolic diet, induce inflammatory reactions and trigger pro-apoptotic events by enhancing the enzymatic activity of colonic NADPH oxidase, with the subsequent increase of ROS intracellular levels. Cell pre-treatment with EGCG fully prevented these processes, essentially by inhibiting NADPH oxidase. Furthermore, this flavanol reduced levels of molecules related to both immune and non-immune responses, namely IL-1α, IL-6, IL-8, MCP-1, IL-23, TGFβ1 and TLR2, suggesting its potential positive regulatory effect in intestinal inflammatory diseases [114, 115].

Flavanones

Flavanones are found in citrus fruits; the most abundant are taxifolin, sinensetin, naringenin and hesperidin. Hesperidin is a β-rutinoside widely consumed in oranges, and its aglycone form is hesperetin [116].

Flavanones are absorbed in the large intestine rather than the small intestine. In general, the bioavailability of flavanones depends on the occurrence of specific microbiota. Hence, alterations of gut microflora affect the pharmacological activities of flavanones.

Few studies are available on the effect of flavanones on intestinal inflammation, and most have focused on the transport of naringerin and hesperidin through the intestinal mucosa layer [117, 118].

Orange extract was administered orally to male Sprague-Dawley rats, and the amounts of available flavanones in the small intestine and colon were measured. An important finding is that flavanones reach the colon where they remain for several hours, enabling them to modify gene and protein expression of the mucosa [119]. TNFα-induced myofibroblast-like cell-line CCD-18Co, derived from a colonic mucosal biopsy, was treated with orange extract, or with a mixture of six major flavanones present in orange extract. Treatment with TNF-α strongly stimulated PAI-1 and MMP-12, and reduced cell migration. These flavonols showed a significant decrease in PAI-1 expression, and a later induction of MMP-12 concomitant with an increase of cell migration.

These results indicate that flavanones can regulate colon fibroblasts, which are critically involved in wound healing and mucosal repair processes during chronic inflammation [119].The anti-inflammatory and antioxidant activity of hesperidin has been shown in a study that used DSS to induce experimental colitis in male BALB/c mice. The health of the animals was evaluated by the Disease Activity Index (DAI). Histopathological and biochemical analyses, together with the DAI, showed that hesperidin improved the health of these animals, lowering oxidative stress and inflammation through an immunomodulatory effect, which involved the suppression of IL-6 and IL-4 [120].

Very interesting results have been reported concerning the importance of these compounds in regulating fatty acid oxidation, and cholesterol and fatty acid synthesis: naringenin was found to activate nuclear receptors PPARα, PPARγ and to suppress their antagonist LXRα in hepatocyte cells[121]. These results are in agreement with the hypothesis that cholesterol oxidation products, i.e. oxysterols, which are LXR agonist, might contribute to inducing intestinal inflammation [115, 122]. In HEPG2 hepatocytes some of these flavanones have been found to decrease cholesterol and triglyceride syntheses, by suppressing the apolipoprotein B [123].

Anthocyanins

Anthocyanins are the pigments contained in red fruits, such as various types of berries, red currants, and grapes. These compounds consist of a molecule of anthocyanidin (the commonest being cyanidin, delphinidin, malvidin, perlagonidin, petunidin, and peonidin) conjugated with one to three sugar residues (the commonest are glucose, galactose, arabinose, rhamnose and xylose) [124].

Unlike other flavonoids, many anthocyanins appear not to undergo extensive metabolism, and their absorption is also influenced by the structure of the type aglycone formed. Further, they undergo re-arrangement in response to pH, being more stable in acidic media [11]. Anthocyanins are only partially absorbed, thus their activity in regard to enterocytes is limited. Because of their chemical similarity, the biological effects of both anthocyanins and anthocyanidins will be discussed in this section.

Most of the studies stress the antioxidant effect of these compounds, but their anti-inflammatory effect has also been extensively seen in tissues other than the gut [125-128].

A randomized study on human subjects consuming purple-flesh potatoes, which contain high quantity of anthocyanins, showed an improvement in serum levels of antioxidant parameters, as well as of inflammation (IL-6 and C-reactive protein) [129]. An *ex-vitro* study showed the radical scavenging activity and antimicrobial activity of bilberry juice and press cake, against *Salmonella* and *Staphylococcus* bacteria in acidic conditions [130]. The effect of the anthocyanin-containing soybean seed coat on suppressing inflammatory responses has been demonstrated in male F344 rats fed with high fat diet and treated with the cancer inducer azoxymethane: soybean significantly reduced ntestinal mucosal COX-2 expression and blood levels of the inflammatory mediator PGE2. Similar results have been obtained in human colon adenocarcinoma HT-29 cell line, incubated with different concentrations of cyanidin, delphinidin, or pelargonidin, in the presence of 12-*O*-tetradecanoylphorbol-13-acetate [131]. Another human colon cancer HCT116 cell line, treated with delphinidin, showed that this anthocyanin induced marked cell-cycle arrest in the G2/M phase, and apoptosis, mainly by activating caspase-3 and inducing poly(ADP-ribose) polymerase cleavage, increasing the expression of pro-apototic Bax protein with a concomitant decrease of anti-apoptotic Bcl-2. Interestingly, delphinidin reduced the activation of NF-κB in HCT116 cells, inhibiting the phosphorylation and degradation of IκBα, and also expression of IKKα, in a dose-dependent manner, meaning that the activity of delphinidin may be focused on NF-κB suppression [132].

PHENOLIC ACIDS

Phenolic acids derive from hydroxycinnamic or benzoic acids. The commonest phenolic acids present in food are hydroxycinnamic acids esterified to a quinic acid, to form clorogenic acids. The most representative compound of this very large class is caffeic acid, mainly present in coffee beverages and propolis. Regular coffee consumers generally ingest 0.5–1 g chlorogenic acid/day, which may be converted to 250–500 mg caffeic acid/day [133].

There are no esterases in human tissues able to release caffeic acid from chlorogenic acids. Consequently, the only significant site for chlorogenic acid metabolism is the colon, where it becomes metabolized by commensal bacteria [69].

Widespread research has revealed the antioxidant and anticancer activity of clorogenic acids. Recent studies focused upon the protective effect of these compounds against the alteration of cell signals related to red-ox imbalance in intestinal inflammation. In the DSS-induced colitis model in C3H/ HeOuJ mice, caffeic acid was found to inhibit iNOS, also decreasing levels of myeloperoxidase. The study authors suggested that the anti-inflammatory effects of caffeic acid might occur through antioxidant mechanisms: dietary supplementation with caffeic acid attenuates IL-17 gene expression, which is directly correlated with decreased iNOS, and with an increase of the anti-inflammatory IL-4. Based on data concerning other tissues, the authors suggested that suppression of the iNOS gene expression by caffeic acid might exert anti-inflammatory effects through NF-κB inactivation. They also hypothesized that the amelioration of colitis provided by caffeic acid treatment could be associated with activation of the cytochrome CYP4B1 gene; this phenol might exert its detoxifying activity by modulating NF-κB, a hypothesis that, however, requires further study [134]. Caffeic acid induced a significant reduction of TNFα and IL-1β, with inhibition of p50 and p65 NF-κB DNA binding, in the colonic mucosa of female Lewis rats, in which colitis had been induced by bacterial peptidoglycan polysaccharide (PG-PS). The induced inflammation resembled that present in Crohn's disease. A reduction of gross colonic injury, and a gain in body weight, have also been observed in PG-PS-treated rats. Similarly, production of TNFα and NF-κB DNA binding, in rat NR8383 macrophages treated with PG-PS, was decreased by cell pre-treatment with caffeic acid. Caffeic acid was also able to inhibit IL-8 production and NF-κB DNA binding, in a TNFα-stimulated SW-620 colonic epithelial cell line [135].

LIGNANS AND STILBENES

Lignans are the main source of phytoestrogens for the Western population, and are present in almost all whole-grain cereals, sesame and flax seeds. Their metabolism is similar to that of isoflavones. Conversion of plant lignans to mammalian lignans occurs in the gastrointestinal tract, as a result of bacterial action. The plant lignans secoisolariciresinol and matairesinol are the dietary precursors of the mammalian lignans, enterodiol and enterolactone. Enterodiol can be further oxidized to enterolactone [136].

Lignans have been investigated in depth for their estrogenic effect. Flax lignans have been hypothesized to be protective against different cancers, included colon cancer [for a review see 137]. Therefore, most studies on lignans and intestinal damage have been in cancer field, in experimental carcinogenesis rat models. It has been found that secoisolariciresinol diglycoside reduced the number of aberrant crypts, in the distal colon of rats injected with azoxymethane as carcinogen, being rapidly converted by bacterial β-glucuronidase to the active lignan [138]. The anti-tumor activity of these compounds has been ascribed to their effect on the regulation of apoptotic and proliferative cell signals [139, 140]. The latter study showed that sesame was able to suppress gene products related to cell survival and

proliferation, such as Bcl-2, survivin, cyclin D1 and COX-2, in human epithelial colon cancer HCT116 cells treated with TNFα. The suppression of these proteins was related to inactivation of NF-κB nuclear binding, suggesting this nuclear factor as the main target of lignan's action.

An interesting finding is that ER-β was able to regulate the expression of cellular adhesion molecules, such as α-catenin and plectin, and likewise cytokeratin 20, a marker of differentiation. The study suggested lignans as possible regulators for maintenance of the normal colonic crypt-villus architecture in the inflamed bowel, through their ER-β-agonism activity [141].

The commonest **stilbene** is resveratrol, which is widely distributed in the plants, and in particular in the skin of red grapes, in certain berries, and in peanuts.

Resveratrol is recognized for its health-beneficial effects as a potent antioxidant and anti-inflammatory molecule that modulates different cell signals in several inflammatory diseases and cancers (for a comprehensive review see [142]).

Most clinical trials have focused on characterizing of the pharmacokinetics and metabolism of resveratrol; despite relatively efficient absorption, its bioavailability is very low, however, because it is metabolized very quickly. Its biological effects are thus limited [143].

A number of studies regarding the anti-inflammatory role of resveratrol in the gut have employed experimental colitis-induced in mice and rats. Resveratrol was found to reverse the decrease of body weight and colon length associated to colitis. It suppressed colitis-induced inflammatory molecules, namely TNFα, IL-6, IL-1β, iNOS, COX-2 and PGES-1, in C57BL/6 mice treated with DSS [144, 145]. The resveratrol-mediated reduction of PGES-1, COX-2 and iNOS appeared to involve down-regulation of p38 MAPK [145]. In addition, after treating colitic rats with resveratrol, the percentage of neutrophils and CD4^{+} T cells, in mesenteric lymph nodes and in the colon lamina propria, was decreased [144]. The suppression of CD3^{+} Th cells, which express TNFα and IFNγ, has also been reported [146]. The negative regulation of NF-κB activity by SIRT-1 has been proposed [144]. This protein has been found to be up-regulated by resveratrol [147].

In another model of DSS-associated colitis in male Fischer F344 rats, a diet with a dose of resveratrol mimicking the normal human intake (rats were fed 1 mg/kg/day resveratrol for 25 days) not only reduced mucosal inflammatory markers (PGE-2, COX-2, PGES-1), but also increased colonic bacteria *Bifidobacterium* and *Lactobacillus*, preventing tissue colonization and invasion by enterobacteria, including *Escherichia coli* [148].

Piceatannol, a tetrahydroxy-trans-stilbene, drastically reduced inflammatory cytokines, phophorylated colonic STAT-3, and p65 NF-κB protein, in BALB/c mice exposed to DSS, suggesting this stilbene may prevent intestinal inflammation [149].

Another stilbene, pterostilbene, has been found in several types of blueberries, and in unripe Pinot noir grapes. Its structural difference from resveratrol may contribute to its better bioavailability. Pterostilbene blocked the activation of p38 MAPK signaling, whereas it exerted no effect on the NF-κB and JAK-STAT pathways, in HT-29 cells treated with a pro-inflammatory mixture of TNFα, IFNγ, and with LPS [150]. On the contrary, pterostilbene has been found more effective than resveratrol in reducing aberrant crypt foci, lymphoid nodules, and tumors in male BALB/c mice, in which experimental colon cancer had been induced by azoxymethane. Pterostilbene was able to reduce NF-κB activation, by inhibiting phosphorylation of PKC-β2 and decreasing downstream target gene expression, for example iNOS, COX-2 and aldose reductase. Moreover, pterostilbene significantly enhanced the expression of the antioxidant enzymes, heme oxygenase-1 and glutathione reductase, by activating antioxidant signaling dependent on Nrf2 transcription factor [151].

CONCLUSIONS

The pathophysiology of IBD is still not fully understood, but it is widely accepted that immunologic, environmental, and genetic factors concur to determine its clinical manifestations.

More recently, it has been suggested that human IBD may be the result of abnormalities of the host immune system or of the gut flora. It has been shown that intestinal colon mucosa of IBD patients is dominated by T cell and macrophage infiltrates, producing cytokines and chemokines, which amplify and perpetuate local inflammatory and oxidative reactions.

IBD management often entails long-term treatment to control the disease, based on a combination of drugs. The classical therapeutic approach requires anti-inflammatory agents, such as aminosalicylates and corticosteroids, which usually provide significant suppression of inflammation and rapid relief of symptoms. However, they often bring poor results, and the disease becomes refractory. Recent pathophysiological considerations have led to more specific drugs being used, such as immune modulators or anti-TNFα antibodies, but all bring a risk of important side effects and poor response. The outcome is that surgery is required limiting the quality of life of the patients.

Besides their proven antioxidant qualities, polyphenols show health-promoting effects, because of their marked ability to modulate inflammatory and immune responses. In particular, most of them mainly target the activity of the red-ox transcription factor NF-κB, which controls the cell signaling cascades that are crucial in the development of IBD. They should thus be used as natural dietary chemicals, able to mimic the action of pharmaceuticals in IBD.

Several studies on experimental models have shown that polyphenols, or their plant extracts containing them, were able to reduce colonic injury; however, knowledge of the beneficial effect on human intestinal inflammation is not yet sufficient.

The gut is mainly exposed to polyphenol absorption and metabolism; their concentration in the intestinal mucosa should thus logically be much higher than in other tissues. In addition, several unknown metabolites with possible biological activity are thought to be produced by the intestinal tissue, or by colonic mucosa. The so-called prebiotic activity of polyphenols, whereby they are able to induce changes in the colonic bacterial population, is an emerging and interesting field.

It should be remembered that, since IBD patients often require extensive surgical resection of the gastrointestinal tract, they frequently have severely impaired intestinal absorption, and altered microflora composition. Thus, the large inter-individual variation in polyphenol metabolism, depending at least partly on the functional surface area of the intestinal mucosa, must be clarified.

Polyphenols may be of interest as compounds able to prevent or delay the progression of IBD, or for use as possible adjuvants, in patients who are resistant or intolerant to the commonly-used steroids.The currently-reported studies assessing the effectiveness of polyphenols in IBD treatment suggest interesting perspectives; they are still too limited in number, however, and long-term confirmation remains to be provided.

ABBREVIATIONS

ADP: Adenosine diphosphate

AKT: serine/threonin protein kinase (v-akt murine thimoma viral oncogene homolog1)

AP1: activator protein 1

Bcl-2: B-cell lymphoma 2 anti-apoptotic protein

CD4+; CD25+: cluster of differentiation 4+;25+

COX: cyclooxygenase

CpG: cytosine nucleotide next to guanine separated by a phosphate

DSS: dextran sodium sulfate

ERK: extracellular signal regulated kinase

FOXP3: forkhead box protein 3

HIF: hypoxia inducible factor

IFNγ: Interferon gamma

IKK: Inhibitor of NF-kB kinase

IL: Interleukin

IP-10: interferonγ-inducible protein 10

IRF-1: interferon regulatory factor 1

IκBα, IκBβ, IκBε,: Inhibitor of NF-κB subunits

JAK: just another kinase

LPS: lipopolysaccharide

LXR : liver X receptor

MCP-1: monocyte chemotactic protein-1

MEKs: MAP Kinase - ERK Kinase

MIP-2: macrophage inflammatory protein 2

MMP : matrix metalloproteinase

MYD88: myeloid differentiation primary-response gene 88

NADPH: nicotinamide adenine dinucleotide phosphate

NEMO: NF-kB Essential Modulator

NF-E2: nuclear factor (erythroid-derived 2)-like 2

NF-kB: nuclear factor- kappaB

NLR : NOD-like receptor

NOD: nucleotide-binding oligomerization domain

p21: protein 21

p38 MAPK: protein38 mitogen-activated protein kinase

PAI-1: plasminogen activator inhibitor 1

PGE2: prostaglandin E2

PGES-1: prostaglandin E synthase-1

PI-3K: phosphatidylinositol-3 kinase

PKC-β2: protein kinase C β2

PPAR: peroxisome proliferator-activated receptor

RIP2: receptor-interacting protein 2

ROS: reactive oxygen species

SIRT-1: silent mating type information regulation 1, deacetylase protein

STAT-1: Signal Transducer and Activator of Transcription

TGFβ1: Transforming growth factor 1

Th: Thelper

TLR: toll-like receptor

TNBS: trinitrobenzene sulfonic acid

TNFα: tumor necrosis factor alpha

TRIF: TIR-domain-containing adapter-inducing interferon beta

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