Review Article

Antioxidant therapy for treatment of inflammatory bowel disease: Does it work?

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ABSTRACT

Oxidative stress (OS) is considered as one of the etiologic factors involved in several signals and symptoms of inflammatory bowel diseases (IBD) that include diarrhea, toxic megacolon and abdominal pain. This systematic review discusses approaches, challenges and perspectives into the use of non-traditional antioxidant therapy on IBD, including natural and synthetic compounds in both human and animal models. One hundred and thirty four papers were identified, of which only four were evaluated in humans. Some of the challenges identified in this review can shed light on this fact: lack of standardization of OS biomarkers, absence of safety data and clinical trials for the chemicals and biological molecules, as well as the fact that most of the compounds were not repeatedly tested in several situations, including acute and chronic colitis. This review hopes to stimulate researchers to become more involved in this fruitful area, to warrant investigation of novel, alternative and efficacious antioxidant-based therapies.

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1. Introduction

Inflammatory bowel diseases (IBD) are most commonly represented by Crohn's disease (CD), which involves any segment of the gastrointestinal tract, and ulcerative colitis (UC), that occurs in the inner lining of the colon (large intestine) or rectum. IBD is characterized by chronic or relapsing immune activation and
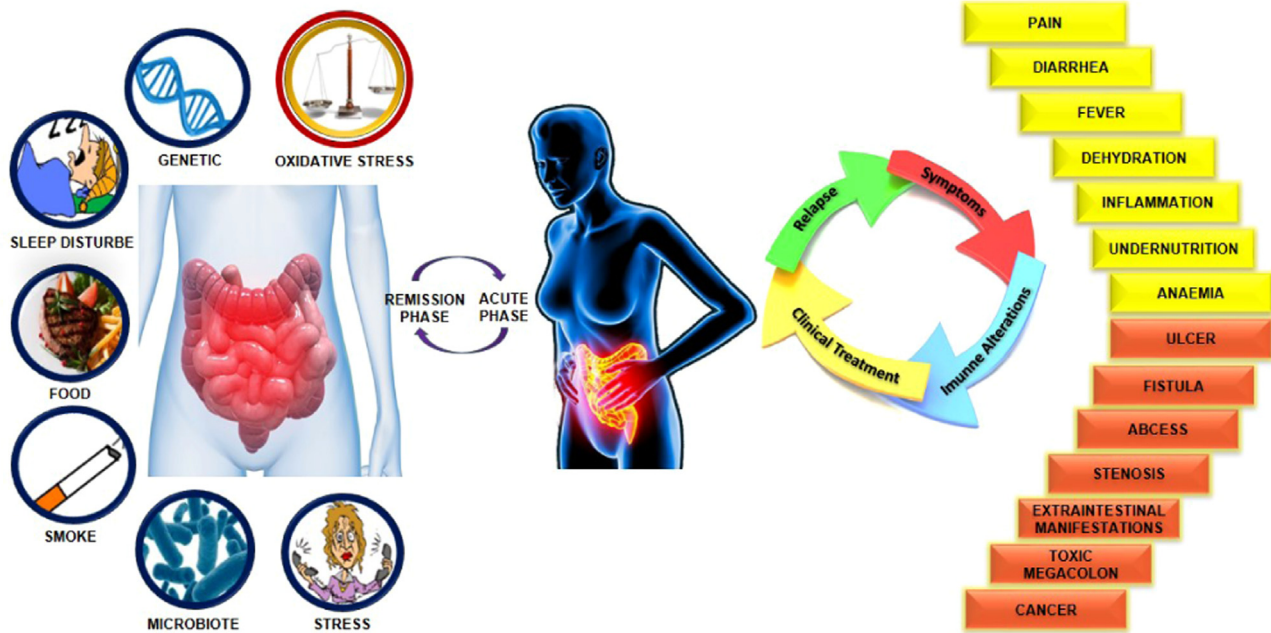
Fig. 1. Important risk factors associated with inflammatory bowel diseases and immunological changes.

inflammation within the gastrointestinal tract [1]. The etiology of IBD remains unclear but environmental factors, as well as infectious, immunological, and psychological ones, together with genetic susceptibility could be the major causes for the onset of UC [2] (Fig. 1). Although the prevalence and incidence of IBD is increasing (150–250/100,000 population), especially in developed countries, it is rarely fatal. It can however, greatly diminish the quality of life because of the pain, vomiting, diarrhea and other socially unacceptable symptoms it causes. The increased risk of colorectal cancer (from 0.5% up to 20% per year) is a serious complication of IBD, particularly in the case of UC [3].

The current therapy for IBD relies on the use of sulfasalazine, corticosteroids, immunosuppressive agents, such as azatriopine, and biological therapy (Fig. 2) represented by the anti-TNFα (tumor necrosis factor alpha) antibody as the mainstream treatment for down-regulating aberrant immune responses and inflammatory cascades [4]. However, the adverse effects associated with these drugs over prolonged treatment periods and the high relapse rate limit their use [5]. Sulfasalazine, for instance, can exacerbate colitis, resulting in diarrhea, abdominal cramps and discomfort [6]. Antibiotics, one of the commonly used therapies, could adversely change the environmental conditions of microbiota and trigger resistance. Moreover, immunosuppressant and anti-inflammatory drugs (such as corticosteroids) have many undesirable side effects [7] and the combined therapy, using corticosteroids plus infliximab does not appear to provide any additional benefit over infliximab monotherapy [8]. Furthermore, these drugs display limited beneficial actions. In the long term, ≤25–33% of patients with UC will require surgery if pharmacological treatments are not successful, or in the case of complications such as fistulae, stenosis, or abscesses (particularly in Crohn's patients) [9]. The potential of these drugs when used over a long period of time, to induce severe side effects, together with the high costs of the therapy for patients, warrant investigation of novel and alternative pharmacological approaches [10].

In recent years, several studies had focused on reactive oxygen species (ROS) and reactive nitrogen species (RNS) as the etiologic factors for IBD [11–14]. The gastrointestinal tract is a major site for

generation of pro-oxidants, whose production is primarily due to the presence of a plethora of microbes, food ingredients and interactions between immune cells [15]. Furthermore, the antioxidant capacity of patients with IBD is reduced, even in the asymptomatic phase of the disease [16]. To scavenge RONS, intestinal cells have several enzymatic and non-enzymatic antioxidants, including superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT), but excessive generation of RONS enhances lipid peroxidation (LP) and could deplete antioxidant defenses [17].

It should be noted that OS is clearly involved in IBD, once immune activation such as inflammation [18] occurs and could be a major contributing factor to tissue injury and fibrosis that characterize CD [19]. In this regard, reduction of plasma antioxidants and total intestinal antioxidant capacity has been observed in CD [20]. Like in CD, several studies have shown oxidative stress in UC. Patients with UC often have antioxidant nutrient deficiencies at the time of diagnosis [21–23] and that could suggest an increase of OS.

In this context, recent studies have suggested that the administration of antioxidants, from different sources, with additional anti-inflammatory action may be beneficial in the treatment of IBD because inflammation is caused by OS and leads to the increase of OS that contributes to tissue damage [24–26].

Several reports on non-traditional therapy for IBD have been published. However, those publications put special emphasis on antioxidant and/or anti-inflammatory activity [25–27] or regulation of gut microbiota [28, 29]. Unlike other published approaches, this review is broader and aims to describe and analyze the effect of functional foods and isolated nutrients, probiotics, natural active compounds from vegetal sources, drugs, hormones and other synthetic substances, all of them reported as antioxidants, in IBD.

2. Methods

In 2009, Rahimi et al. [30] published a systematic review on the use of herbal medicines for the treatment of IBD [31]. These
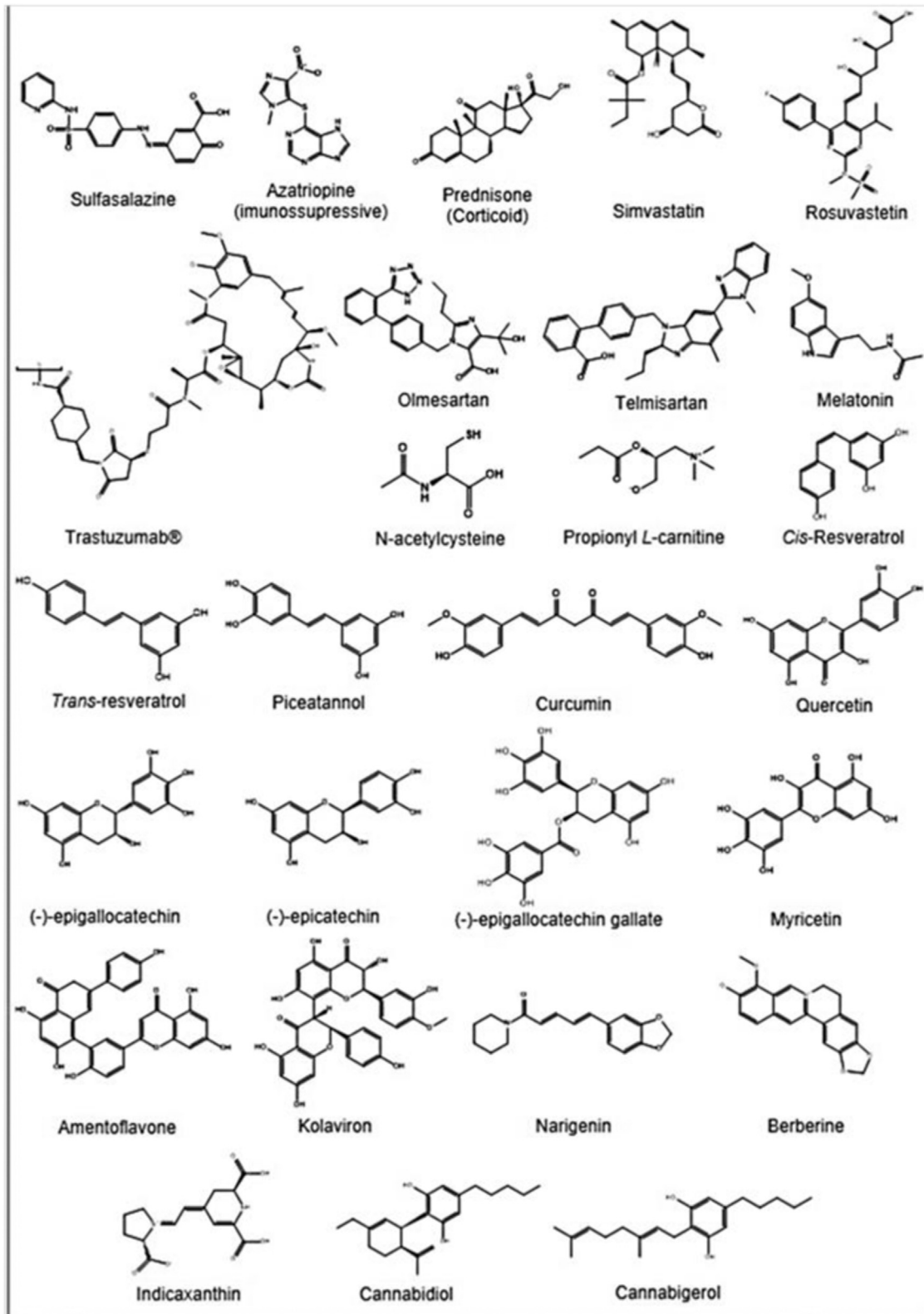
Fig. 2. Main substances used/tested in inflammatory bowel disease therapy (articles published from 2009–2015/06).

authors categorized herbal therapies used to date for UC and CD, and suggested their possible mechanisms of action. After that, several reviews about this topic were published [25,26,32–38], however, up to our knowledge, no one has so far discussed other chemical strategies, applying antioxidants like drugs, polyphenols and others in IBD treatment. In face of that, we reviewed the literature from 2009 up to 2015 (June) to *in vitro* and animal models of colitis induction and without limit of time to human studies, using the keywords inflammatory bowel disease or ulcerative colitis or Crohn disease associated to antioxidant in the databases

of PubMed, ScienceDirect and Scopus. Articles reporting on substances studied *in vitro* or *in vivo* (enemas, oral supplementation or intraperitoneal application) were chosen. To minimize losses, the search was conducted by two researchers, independently.

Initially, the titles of the papers were read, with exclusion of duplicated articles. Thereafter, we identified if the reported work had dealt with antioxidant action (OS biomarkers), using the following phrases:

(1) Scavenging of ROS/RNS ⇒ decrease of the levels of nitrite, nitric oxide (NO$^\bullet$), superoxide anion (O$_2^{\bullet-}$), hydrogen peroxide (H$_2$O$_2$) and others;
(2) Inhibition of RONS synthesis ⇒ decrease of the activity, protein expression or genic expression of inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), NADPH oxidase (NOX), lipoxygenase (LOX), myeloperoxidase (MPO), nuclear factor Kappa-light-chain enhancer of activated B cells (NF-κB) or Iκ-Bα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha);
(3) Inhibition of RONS damage ⇒ biomarkers of LP (thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), 4-hydroxynonenal (HNE) and others), protein damage (protein carbonylation, advanced glycation end-products (AGE) and others) and deoxyribonucleic acid (DNA) damage (8-oxo-2′-deoxyguanosine, 8-oxoguanine and others);
(4) Increase of antioxidant defense (endogenous enzymatic and non enzymatic antioxidant defense and total antioxidant capacity).

Thereafter we categorized the therapies into topics, as following:

(a) Drugs, hormones, synthetic antioxidants and chemicals derived from sources, other than vegetables;
(b) Polyphenols and other natural active compounds from medicinal plants;
(c) Functional foods, antioxidant nutrients and probiotics.

3. Results and discussion

One-hundred and thirty four papers were found. A summary of the method and the total number of articles for each category are displayed in Fig. 3.

In sequence, we will discuss the role of OS in IBD, the major biomarkers used in diagnosis, and the several classes of antioxidants available for IBD treatment.

3.1. Oxidative stress and IBD

OS is defined as an imbalance between oxidants (ROS, RNS) and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage [39]. ROS is generally taken to encompass the initial species generated by oxygen reduction as well as their secondary reactive products, and include free radicals such as the radical anion superoxide O$_2^{\bullet-}$, hydroxyl radical (HO$^\bullet$), peroxyl (RO$_2^\bullet$), alcoxyl (RO$^\bullet$) and hydroperoxyl (HO$_2^\bullet$), and non-radical species such as singlet oxygen (^{1}O$_2$), H$_2$O$_2$ and hydrochlorous acid (HOCl). RNS include free radicals like nitric oxide (NO$^\bullet$), nitrogen dioxide (NO$_2^\bullet$), anions like peroxynitrite (ONOO$^-$), as well as nonradicals such as nitrous oxide (HNO$_2$), nitryl chloride (NO$_2$Cl) and alkyl peroxynitrites (ONOOR) [40].

Gastrointestinal (GI) tract is a key source of ROS production. Despite the protective barrier provided by the epithelial layer, ingested materials and pathogens can cause inflammation by
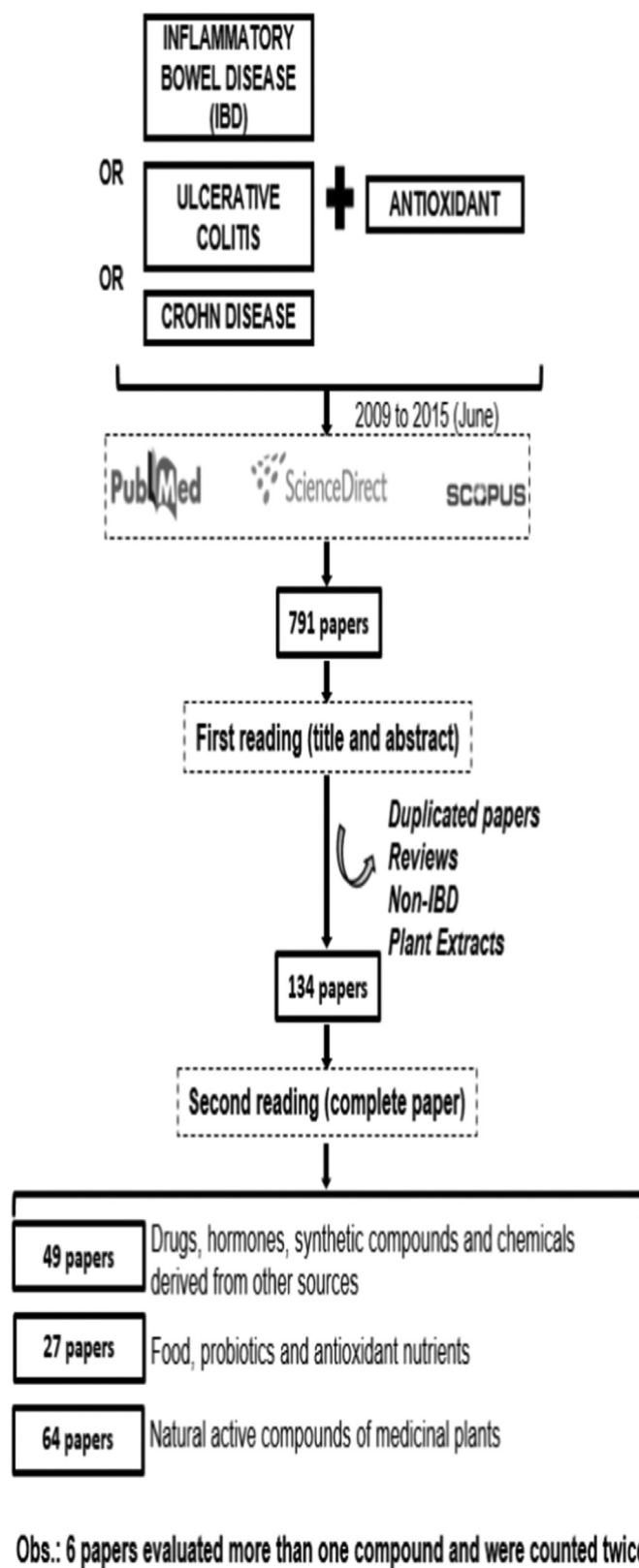

Fig. 3. Main results from the database search.

activating the epithelium, polymorphonuclear neutrophils (PMNs), and macrophages to produce inflammatory cytokines and other mediators that contribute further to OS [41].

Dysfunction of the intestinal barrier accompanied by increased intestinal permeability is another characteristic symptom in the

pathophysiology of IBD [42]. It is believed that the ability of commensal bacteria to adhere to the epithelial layer via oligosaccharides helps deter invasion by displacing pathogenic bacteria [43]. In this context, the increased permeability of gastrointestinal epithelial cells frequently results from the destruction of tight junctions (TJ), and release of different pro-inflammatory mediators, including ROS and RNS, which actively contribute to the pathogenic cascade that initiates and perpetuates the inflammatory response in the gut [44].

The main sites of RONS production in IBD are activated neutrophils and macrophages. During episodes of inflammation, these cells exhibit massive intestinal mucosa infiltration and release large amounts of these species [45]. The enhanced production of RONS is associated with chronic intestinal inflammation in the early stages of IBD, and their destructive effects on DNA, proteins and lipids may contribute to initiation and progression of CD [19] as well as UC [46], resulting in prominent inflammation, increased amounts of cytokines such as tumor necrosis factor (TNF)-α, interleukins IL-6 and IL-1β. Such biological compounds trigger the pathological responses and symptoms of IBD [47]. The increased OS associated with peripheral DNA damage may be one of the pathophysiological mechanisms in the development of UC associated colorectal cancer, together with actin carbonylation and nitration of actin and tubulin which disrupt the cytoarchitecture and cause tissue injury [48].

Another factor involved in the etiology of colitis is the enzyme Glutathione Peroxidase type 2 (GPx2), a gastrointestinal-specific form of GPx. According with a recent review, in contrast to other enzymes such MnSOD and CAT, which had been shown to be modestly reduced in inflamed issue, GPx2 had its expression increased during colitis [49]. An in vitro investigation with tissue of patients with colorectal cancer or UC, had identified that GPx2 is strategically located in endoplasmic reticulum where it can interfere with COX-2 activity by local removal of hydroperoxides and, thus, regulates the level of prostaglandin E 2 (PGE2), considered to be a key mediator of acute inflammatory responses [50]. The relevance of the hydroperoxide level to inflammatory processes in the gastrointestinal system is indeed evident from the spontaneous development of ileocolitis and intestinal cancer in GPx1/2 DKO mice. In this case, a synergism between both enzymes is suggested, but the role of GPx2 appears to be more important, since a single allele of GPx2 but not of GPx1 proved to be sufficient to prevent inflammation in this knockout mice [51]. Therefore, GPx2 activation may prevent undue responses to inflammatory stimuli and, in consequence, inflammation-driven initiation of carcinogenesis

A summary of these alterations is displayed in Fig. 4. In brief, RONS cause intestinal tissue lipid peroxidation, necrosis/apoptosis and epithelial ulcers. These species are also responsible for the disruption of intercellular junctions, as well as leukocyte and neutrophil infiltration that produce ROS, RNS and cytokines that lead to the inflammatory process. Nitric oxide (NO•) acts on chloride anions and stimulates their release into the intercellular medium with a consequent loss of water leading to osmotic diarrhea. NO• also diffuses into the muscle layer and can cause toxic megacolon, a common complication of IBD, especially in the case of UC.

To regulate the destructive effects of RONS, vital tissues are equipped with an intricate antioxidant defense system. These antioxidant control systems consist of enzymes such as SOD, CAT, GPx and peroxiredoxins [52], as well as antioxidant compounds, like α-tocopherol, β-carotene, vitamin C, GSH, bilirubin, urate, zinc, selenium and copper [53]. When this system fails, OS occurs [12]. Increased formation of RONS in the colonic mucosa in animal models of IBD has been known to be correlated not only with disease severity and progression, but also with extra-intestinal manifestations of UC, such as hepatobiliary disorder [54].

Inhibition of both inflammatory mediators and ROS production would provide an important protective and therapeutic treatment for IBD [47,55,56]. Therefore, identifying new antioxidants for IBD treatment has recently attracted much attention worldwide and will be discussed below.

For instance, some authors observed no difference [57], decreased [58] or increased levels [14], in plasma/erythrocyte, of antioxidant enzymes in patients with active intestinal inflammation. In a study [16], the authors showed significant modifications regards levels of OS markers in the serum of patients with active IBD, such as decreased SOD and GPx activity, and a low antioxidant profile and increased lipid peroxidation in patients in the remission phase. In tissue biopsies, an increase of malondialdehyde (MDA) was found, in both UC and CD patients [59] and reduced GPx and glutathione (GSH) activity/levels in inflamed CD mucosa [60]. A possible explanation given by the authors for low GPx and SOD in remission patients is the consumption of antioxidants present in the diet or supplementation during active phases. Another and more tempting hypothesis is that the patients suffering from IBD, even if they are in remission, have a low antioxidant defense, i.e. a pre-existing redox imbalance condition [18].

Despite the difficulty of comparing antioxidant capacity, due to the use of different methods, single versus chemical products in mixture, one table, listing chemicals, pure and in mixture, functional foods, and others, is herein included and the main biomarkers of OS analyzed (see Table 1). There are several controversies and contradictory results, which point out to the necessity of further experimental research.

The relationship between colitis and cancer is also associated to activation of common tumor-related signaling pathways, including mutations of the p53 gene, the most frequently reported somatic gene alterations in human cancer, leading to accumulation of p53 gene products in tumor cells that can initiate an immune response with generation of circulating anti-p53 antibodies (p53Abs) [61]. Several studies have demonstrated that p53 overexpression is found in IBD patients and this fact is closely associated with neoplasia, especially in those with mucosa dysplasia [62]. The p53 activation is intrinsically associated with OS, by inducing the expression of p85, which may function as a signaling molecule during ROS-mediated p53-dependent apoptosis. p85 is a known regulator of phosphatidyl inositol-3 kinase (PI3K); however, its function during ROS-induced apoptosis is independent of PI3K [63]. p53 also induces $NO^{•-}$ cellular stress, and chronic inflammation, as well as elevated levels of the inducible nitric oxide synthase (iNOS) and increased TP53 mutation [64]. Staib et al. [65] identified 14 common genes among NO•, H_2O_2, DNA replication arrest, and hypoxia, and interestingly 8 of them are known as p53 target genes [65].

3.2. Oxidative stress biomarkers

As previously mentioned, OS is a crucial pathophysiological factor for human IBD. It is therefore important to identify the best biomarkers for the diseases, in order to verify whether the applied therapy is effective or not, in controlling the symptoms of IBD. Antioxidant enzymes such as SOD, GPx and CAT, and the non-enzymatic sulfhydryl groups play a major role in the organism defense against excess RONS generation, but changes in this profile seem to be the most difficult to quantify when looking at the various studies done on IBD. In fact, the identification of OS biomarkers is an important challenge to the scientific community as well as the analysis of the sensitivity of these biomarkers in the several biological matrixes (urine, blood, and tissue etc.) and how analytical procedures can compare, appropriately, each of these biomarkers [66].
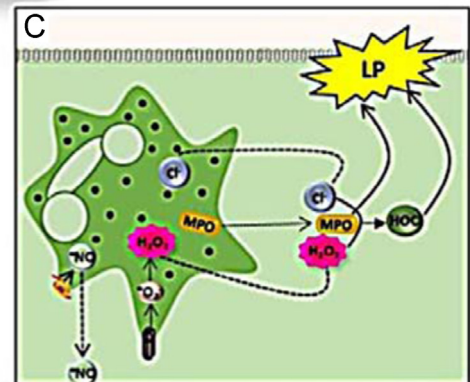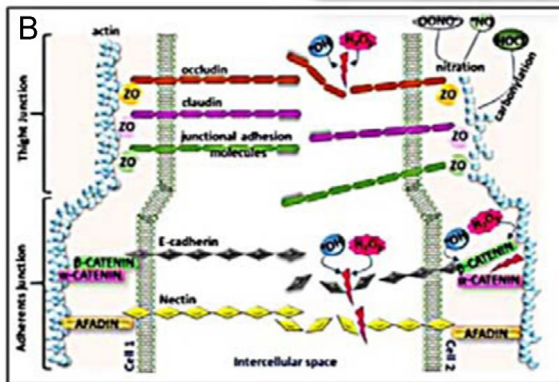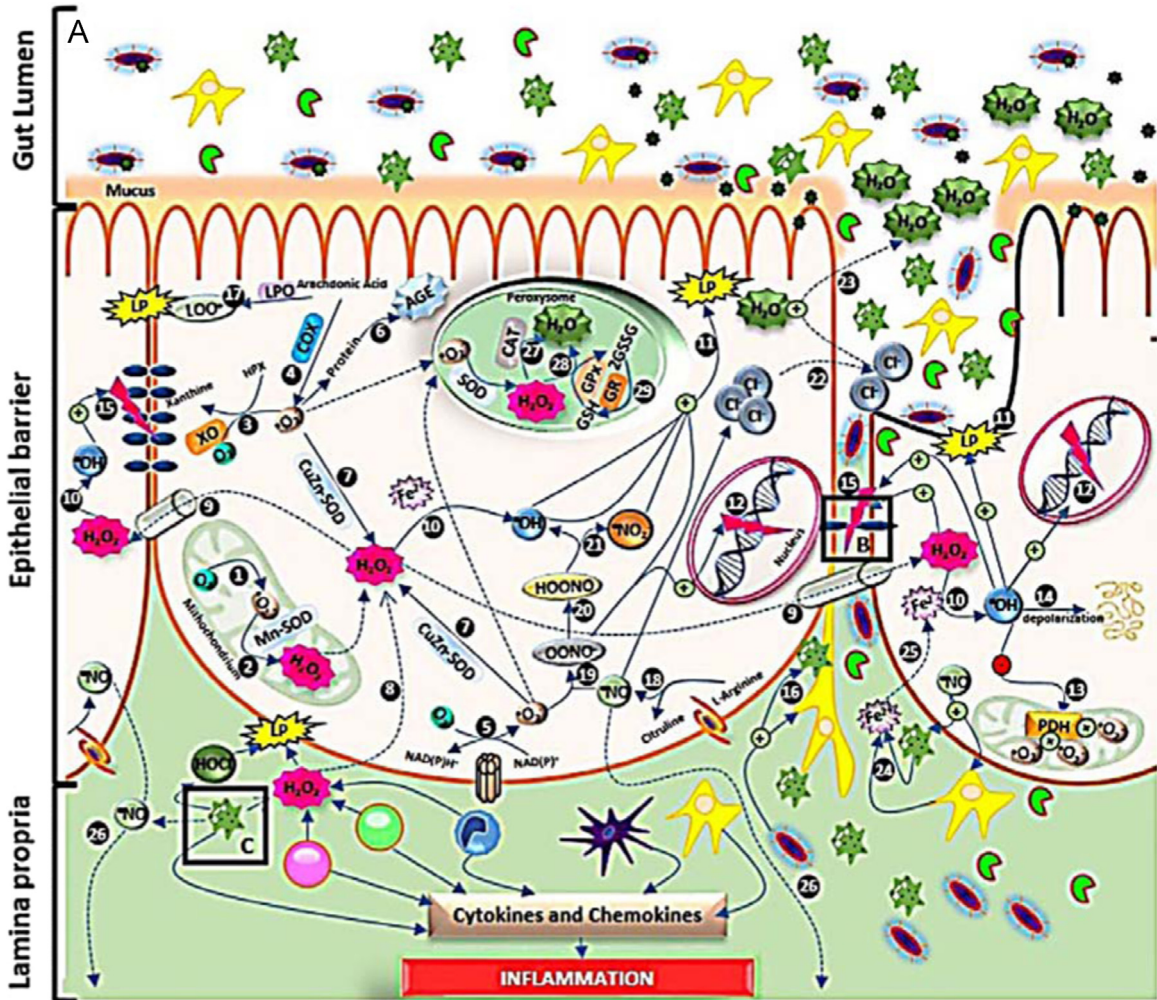
As it has been said, UC and CD subjects exhibit increased LP [59], and for that, MDA or thiobarbituric acid reactive substances (TBARS), an indirect measure of MDA, is extensively used as a biomarker for oxidative damage. However, because other biological materials may react with thiobarbituric acid, resulting in high TBARS levels, this marker is under scrutiny. Other molecules derived from LP, such as hydroperoxides, isoprostanes, conjugated dienes and others have been used by the scientific community, but like MDA, have advantages and limitations [67]. Among these molecules, F2-isoprostane, measured by mass spectrometry, has been the best general indicator of non-enzymatic lipid peroxidation under normoxic conditions [68]

Myeloperoxidase (MPO), a heme protein secreted by phagocytes, especially neutrophils, is a marker for local leukocyte sequestration and inflammation. An increase in MPO activity and the generation of NO$^\bullet$ has also been demonstrated in inflamed colon biopsies and both are related to the disease's progression [69]. Reports have demonstrated a significant correlation with other OS markers, such as MDA and H_2O_2, in patients with metabolic syndrome [70]. In bowel, MPO is present in neutrophils and macrophages derived from inflamed mucosa infiltration in the damaged area and rupture of the colonic barrier. They produce both inflammatory mediators (cytokines and chemokines) and OS through the generation of HOCl and oxidation of the unsaturated fatty acids present in the plasma membrane [71] (Fig. 4). Furthermore, MPO levels are found to be elevated in malignant tissues, suggesting that MPO-derived oxidants play a role in colon cancer [72].

For Hartmann, besides lipid peroxidation, the increase of iNOS expression and consequently NO$^\bullet$ levels in rats, was associated with a significant decrease in anal sphincter pressure [73] and consequent increased diarrhea and other IBD symptoms.

Furthermore, these compounds cause damage to cells of the mucosa and submucosa of the bowel [74]. iNOS is represented by three isoforms of NOS and is found in macrophages and smooth-muscle cells. It allows the production of NO$^\bullet$ in large quantities as part of the mechanism of cell death in response to lipopolysaccharides, cytokines, and glucocorticoids. As such, this enzyme and its metabolites are involved in septic shock and inflammatory disorders [75].

Another common metabolite, GSH, has been used as an alternative indicator of both inflammation and OS, once its intracellular levels suffer modification due to its action in the extracellular pool, which is related with its function in detoxification and protection of cells from chemical- and oxidant-induced injuries [76]. In inflammatory diseases, for instance, the rate of consumption of GSH may increase dramatically [77]. For IBD subjects, contradictory results have been reported in terms of both GSH levels and GSH/GSSG ratio. In colon biopsies, either a decrease [78] or no changes in GSH levels [79], along with an increase in GSSG levels [78] had been detected. In fact, in animal colitis models, GSH levels are normally reduced [80–82].

According to Sakthivel et al. [83], SOD levels increase in UC induced by intrarectal acetic acid. The elevation of SOD and other antioxidants can be explained by the fact that in IBD, inflammation and OS are present and this SOD increase would protect the tissue against oxidative damage. However, in studies on UC induced by acetic acid [82,84] and TNBS [81,85,86], SOD activity was reduced, which clearly indicates increased levels of OS, which may damage cells through lipid peroxidation of membranes and oxidation of cellular proteins [84]. Similar results were observed for GPx. According to Rabelo Socca et al [81] and [87], GPx activity in rats with UC induced by TNBS, increased, whereas for Mueller et al., in a DSS (dextran sulfate sodium) UC model, this enzyme activity was

Fig. 4. Oxidative stress and its association with the physiopathological process of IBD.

Legend description: reactive oxygen species (ROS) are produced through several metabolic pathways. (1) In mitochondria, during the respiratory process, the electron transport chain normally transforms 2–3% of O_2 to $O_2^{\bullet-}$ (complex I and III). Then, this reactive species undergoes dismutation by Mn-SOD and generates (2) H_2O_2. In the cytosol, $O_2^{\bullet-}$ can be generated by (3) xanthine oxidase (XO), (4) cyclooxygenase 2 (COX2) and (5) NADPH oxidase (NOX) and generates (6) advanced glycation end-products (AGE) that are involved with the inflammatory process, or can form (7) H_2O_2 by CuZn–SOD. Hydrogen peroxide can be also produced by (8) immune cells: monocytes, lymphocytes and (A) neutrophils (principally), coming from leukocyte infiltration that is characteristic of IBD. The reactive molecule H_2O_2, unlike the $O_2^{\bullet-}$, is long lived and highly biomembrane permeable, facilitated by the (9) aquaporin-8 channel. In the cytosol, together with metals such as Fe^{2+}, Cu^{2+}, Co^{2+} and Cr^{2+}, and by (10) the Fenton and Haber-Weiss reactions, H_2O_2 forms the hydroxyl radical (HO$^-$) which is highly toxic and can directly cause (11) lipid peroxidation (LP). Other actions by HO$^\bullet$ are: (12) DNA fragmentation, (13) inactivation of mitochondrial pyruvate dehydrogenase (PDH), (14) mucin depolarization and (15) destruction of (B) apical intercellular junctions. These damaging actions cause (11) tissue disruption and cellular death and then ulcerations in the mucosa, typical IBD damage; (12) mutagenesis and cancer; (13) increased mitochondrial $O_2^{\bullet-}$ generation and OS, which has a direct relationship to the severity of the disease; (14) decreased formation of the mucous layer and promotion of (15) bacterial translocation, which stimulates macrophages and neutrophil recruit, as well as increased intestinal permeability; and facilitates (16) leukocytes and neutrophil infiltration, causing inflammation. Another enzyme present in the cytosol, lipoxygenase (LPO) also causes LP via (17) lipoperoxide (LOOH) formation.

All reactive nitrogen species (RNS) are formed from nitric oxide (NO$^\bullet$), produced by (18) inducible nitric oxide synthase (iNOS) that converts L-arginine to L-citruline. The NO$^\bullet$ reacts with $O_2^{\bullet-}$ to furnish (19) the peroxynitrite anion (ONOO$^-$), which then becomes (20) peroxynitrous acid (ONOOH). The latter then generates the new species (21) of nitrogen dioxide (NO$_2^\bullet$) that causes LP. ONOO$^-$ is highly reactive and can cause (12) DNA fragmentation and RNS/ROS stimulation (10) of LP. Nitric oxide has dangerous actions on enterocytes. This gas stimulates (22) chloride secretion to the mucosa with a consequent (23) water release into the intestinal lumen causing osmotic diarrhea, the most frequent symptom of IBD. RNS are chemotactic mediators of macrophages and neutrophils that (24) stimulate ferrous release from defense cells (25) into the intracellular environment. Nitric oxide, despite having a half-life of $\cong$ 3 s, can (26) diffuse to the muscle layer (smooth muscle) and causes no-cholinergic and no-adrenergic relaxing and consequently toxic megacolon, a common clinical complication of IBD.

Because of disrupted permeability, antigens derived from food digestion and from commensal or pathogenic bacteria can overcome the unprotected mucosal barrier and provoke a continuous intestinal immune response that then causes tissue damage. The inflammatory response often results in continued epithelial injury, which causes erosions and ulcerations leading to an increased exposure to intestinal microbiota and amplification of the inflammatory response.

Antioxidant cell defenses involve enzymes and non-enzymes present in peroxisomes. In this organelle, H_2O_2 can be transformed into water (H_2O) by (27) catalase (CAT), principally in the inflammatory process, and (28) by glutathione peroxidase (GPx). For peroxisomes to obtain GPx there is a need to convert reduced glutathione (GSH) to its oxidized form (GSSH). For regeneration of GSH, the presence of (29) glutathione reductase (GR) – glutathione cycle is necessary.

Adapted from Refs. [46,71,132].

A – Disruption of intercellular junctions

The intercellular junctions of the intestinal epithelium are constituted of tight junctions (TJ), adherent junctions (AJ), and desmosomes. The epithelial tight junctions form a barrier to the entry of allergens, toxins and pathogens across the epithelium into the interstitial tissue. ROS and RNS can promote disruption of both, TJs and AJs. NO$^-$ and ONOOH cause nitration of actin present in the cell cytosol. Concomitant to RNS, $H_2O_2^\bullet$ and HO$^\bullet$ can cause dephosphorylation (serin/thyrosin) or phosphorylation (thyrosin) of occludin – connected to actin by ZO (*Zonula occludens*) (1, 2 or 3) proteins – and phosphorylation (tyrosine) of β-catenin – which connect E-cadherin with α-catenin and this to actin. Both, actin rearrangement (caused by nitration) and (de)phosphorylation of adherent/linker proteins, promote disruption of intercellular junctions, barrier dysfunction and consequent increase of intestinal permeability to neutrophil and bacterial/toxin infiltration and hence the inflammatory processes.

B – Neutrophils and OS

Neutrophils are the principal ROS and RNS sources during the inflammatory process. These cells produce $O_2^{\bullet-}$ from NOX and NO$^\bullet$ from iNOS. H_2O_2 and Cl$^-$ are produced by the myeloperoxidase (MPO) enzyme, which leads to the production of hypochlorus acid (HOCl). Both MPO and HOCl cause LP and tissue damage.

Adapted from Refs. [19,71].

Table 1
Compounds and mixtures of compounds with antioxidant effects tested in inflammatory bowel disease: articles published from 2009–2015/06.

Compounds	Molecular mechanism/ plant origin	Refs	↓RONS		↓ RONS synthesis				↓ RONS damage			Improved antioxidant defense					
			NO•	ROS	iNOS	COX2 LPO NOX	MPO	NF-κB /Iκ-Bα	LP	PTN	DNA	SOD	CAT	GPX	GR GSH GST	Nrf2	AOC
Drugs																	
Telmisartan	Angiotensin II receptor antagonist	[99]	X		X	X		X	X			X		X	X		X
		[100]					X		X								
Olmesartan		[251]					X		X						X		
Rivastigmine	Cholinergic agent	[252]					X		X								
Aminoguanidine	Selective iNOS inhibitor	[154]			X		X		X								
Sildenafil citrate (Viagra)	Therapy for erectile dysfunction terase	[253]					X		X						X		
		[254]					X		X						X		
Setarud (IMOD)	Immunomodulator	[167]					X		X								X
Carvedilol	Nonselective β-adrenoceptor blocker	[255]	X						X		X	X	X	X	X		
Spironolactone	Aldosterone receptor antagonist	[256]		X			X	X									
Fluvoxamine	Selective serotonin reuptake inhibitors	[257]					X										
Fc11a-2 (1-ethyl-5-methyl-2-phenyl-1H-benzo[d]imidazole)	–	[258]					X										
Sinvastatin	Inhibitor of hydroxymethylglutaryl COA reductases	[101]					X		X			X			X		
Rosuvastatin		[101]					X		X			X			X		
Amlodipine	Calcium channel blockers	[259]					X		X			X					
Lazaroid U-74389G	Nonglucocorticoid analogs of methylprednisolone	[260]					X		X						X		
Hormones																	
Melatonin	Sleep metabolism	[104]				X	X	X	X						X	X	
		[96]				X			X						X	X	
		[234]						X	X								
		[109]					X					X					
		[108]		X													
Ghrelin	Stimulation of appetite and gastrointestinal motility	[261]					X		X						X		
Adrenomedullin	Gastrointestinal peptide	[262]	X			X	X										
Synthetic compounds																	
N-acetylcysteine (NAC)		[120]	X				X		X				X		X		
		[235]	X		X	X											
		[236]													X		
		[237]					X		X			X			X		
		[238]		X			X		X						X		
Bis(1-hydroxy-2,2,6,6-tetramethyl-4-piperidinyl) decandioate		[239]					X										
		[240]					X		X								
3,4-Oxo-isopropylidene-shikimic acid (ISA) (derivative of shikimic acid (*Illicium verum* Hook))		[241]	X		X		X		X								
		[242]			X	X	X	X	X			X		X			
		[243]	X		X		X		X			X		X			
3-(3-Pyridylmethylidene)-2-indolinone		[93]						X								X	
Chito-oligosaccharides		[263]			X	X	X	X									
Peptide P-317		[264]					X										
Chemicals derived from sources other than vegetals																	
Superoxide dismutase recombinant *Lactobacillus fermentum*		[126]				X	X	X			X						
Lecithinized superoxide dismutase		[124]				X	X										
Lipoic acid		[55]			X	X	X	X						X	X		
Citicoline		[265]				X			X						X		
Propionyl-*L*-carnitine		[128]	X			X											
Butyrate, *Lactobacillus casei*, and L-carnitine		[266]				X		X								X	
Methylsulfonylmethane (dietary supplement)		[267]				X		X				X		X			
Spirulina (dried biomass of *Arthrospira platensisa*-microalgae)		[248]				X											
		[247]				X		X				X	X	X			
Dunaliella salina (microalgae)		[247]				X		X				X	X	X			
Aspergillus nidulans (fungus)		[268]															
Inonotus obliquus (fungus)		[269]		X		X											
Ursodeoxycholic acid (secondary bile acid)		[270]		–	–	–											
Polyphenols																	
Colon specific resveratrol		[137]				X											
Trans Resveratrol		[138]				X											
		[244]				X			X			X			X		

Table 1 (*continued*)

Compounds	Molecular mechanism/ plant origin	Refs	NO•	ROS	iNOS	COX2 LPO NOX	MPO	NF-κB /Iκ-Bα	LP	PTN	DNA	SOD	CAT	GPX	GR GSH GST	Nrf2	AOC
			↓RONS		↓ RONS synthesis				↓ RONS damage			Improved antioxidant defense					
Resveratrol		[140]				X											
		[142]			X	X											
		[135]*						X									
		[141]	X				X		X						X		
		[143]			X			X									
Piceatannol (hydroxylated analog of resveratrol)		[143]			X			X									
Caffeic acid		[271]					X										
4-Vinyl-2,6-dimethoxyphenol (canolol)		[11]	X			X					X					X	
Verbascoside		[272]			X		X		X								
Ellagic acid		[273]			X	X	X	X									
		[274]			X	X		X									
β-Sitosterol, campesterol, stigmasterol and brassicasterol		[32]							X								
Curcumin		[151]	X				X		X						X		
		[152]					X		X			X	X	X			
		[153]	X				X										
		[154]			X		X		X								
Coumarin		[246]					X		X						X		X
		[76]					X		X						X		
		[245]					X								X		
Apple polyphenols extract		[275]				X											
Green tea polyphenols		[276]													X		
Epi-gallocatechin-3-gallate plus 1-piperoylpiperidin (piperine)		[277]					X		X								
Piperine		[278]	X				X		X			X			X		
Peracetylated epi-gallocatechin-3-gallate		[163]			X	X		X									
Epi-gallocatechin-3-gallate		[279]					X										
Proanthocyanidins from grape seeds		[165]					X	X									
		[166]						X				X		X	X		
		[85]			X		X	X				X					
Quercetin		[155]	X						X						X		
		[156]					X								X		X
		[280]	X				X		X						X		
Diplacone		[281]				X						X	X				
Mimulone		[281]				X											
Amentoflavone		[83]			X	X			X			X			X		
Myricetin		[172]	X				X		X			X		X			
Naringenin (4,5,7-trihydroxyflavonone)		[170]	X						X			X	X				
Kolaviron		[171]	X	X					X			X	X		X		
3′-Hydroxy-5,7,4′-trimethoxyflavone from Zeyheria montana		[282]					X								X		
Other natural active compounds of medicinal plants																	
Thymoquinone	Nigella sativa	[283]					X		X						X		
Sesamol (phenolic derivate)	Sesamum indicum	[284]	X				X		X								
Indicaxanthin (pigment)	Opuntia ficus-indica	[177]	X	X	X	X		X									
Ginsenoside Rd	Panax notoginseng	[285]	X		X		X					X		X			
Iridoid glycosides	Folium syringae	[286]	X				X	X	X								
Embelin (quinone)	Embelia ribes	[287]	X		X		X										
		[288]				X	X								X		
Sanguinarine (alkaloid)	Sanguinaria canadenses and Argemone mexicana	[289]					X	X									
Taurohyodeoxy-cholic acid	Pulvis fellis suis	[290]					X										
Berberine (alkaloid)	Coptidis japonica and Mahonia aquifolium	[178]			X	X	X		X			X	X		X		
Cannabigerol	Cannabis sativa	[179]	X	X	X		X					X					
Cannabidiol		[180]	X	X	X				X								
3,3′-Diindolylmethane	Brassica	[291]															
Flavanolignan	Sylmarin (Silybum marianum)+Selenium nanoparticles	[292]					X	X	X	X					X		X
Aloin (anthraquinone) Aloesin (chromone)	Aloe vera Aloe-gel	[293]					X										
Oligonol	17.6% of catechin-type monomers and 18.6% of proanthocyanidin dimers and trimers	[294]			X	X		X	X			X		X			
Cavdina	Corydalis impatiens	[295]					X	X	X			X			X		
Fraxinellone (lactone)	Cortex dictamni	[296]	X	X	X			X									

Table 1 (continued)

Compounds	Molecular mechanism/ plant origin	Refs	↓RONS		↓ RONS synthesis				↓ RONS damage			Improved antioxidant defense					
			NO•	ROS	iNOS	COX2 LPO NOX	MPO	NF-κB /Iκ-Bα	LP	PTN	DNA	SOD	CAT	GPX	GR GSH GST	Nrf2	AOC
Asiatic acid (triterpenoid compound)	Centella asiatica	[297]		X			X										
Isatin (1H-indole-2,3-dione)	Heterocyclic compounds found in various medicinal plant species	[81]				X	X					X		X	X		
Allicin	Garlic	[298]				X	X	X	X			X	X	X	X		
Functional food and nutrients																	
Camel's milk		[31]					X								X		X
Extra virgin olive oil diet enriched with hydroxytyrosol (polyphenol)		[199]			X	X	X	X									
		[195]			X	X											
		[188]			X	X											
		[299]			X	X		X									
		[300]			X	X	X	X									
		[301]			X	X											
Vitamin E		[47]				X			X			X			X		
Selenium and vitamin E		[209]				X							X				X
Vitamin C, vitamin E, and glutathione		[210]				–			–	–					X		
L-arginine and gallic acid		[302]	X						X			X	X		X		
Anti TNFα+zinc acetate		[214]					X										
Coenzyme Q10		[259]					X		X			X					
Lacto-wolfberry (formulated product of wolfberries in skimmed milk)		[303]		X		X		X						X		X	
Vitamins C and E		[215]*							X								
Vitamin C, vitamin E, β-carotene, zinc, selenium and glutamine		[216]*									–				–		
Probiotics																	
Recombinant probiotic		[230]							X#	X#							
Modified Lactobacillus casei BL23 strains		[220]										X	X				
L. delbrueckii subsp. bulgaricus B3 strain; L. delbrueckii subsp. bulgaricus A13 strain		[227]							X			X	X	X	X		
Lactococcus lactis subsp. cremoris FC		[304]			X			X									
Ultrabiotique® (Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium lactis and Bifidobacterium breve).		[228]	X														
Lactobacillus fermentum		[229]					X										
TR5 (Streptococcus thermophilus, Lactobacillus reuteri, Bifidobacterium bifidium, Latobacillus acidophilus, and Latobacillus casei)		[305]		X	X	X	X	X	X			X					
Lactobacillus pentosus var. plantarum C29		[306]		X	X	X		X	X						X		
Lactococcus lactis		[307]		X								X					
Ultrabiotique® (L. acidophilus, L. plantarum, B. lactis and B. breve)		[308]	X		X			X									
Lactobacillus plantarum 21		[309]	X						X						X		
Butyricicoccus pullicaecorum		[310]					X										

AOC=antioxidant capacity; CAT=catalase; COX2=cyclooxigenase type 2; DNA=deoxyribonucleic acid; GPx=glutathione peroxidase; GR=glutathione reductase; GSH=glutathione; GST=glutathione S-transferase; iNOS=inducible nitric oxide synthase; Iκ-Bα=nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; LP=lipid peroxidation; LPO=lipoxygenase; MPO=myeloperoxidase; NF-κB=Nuclear Factor Kappa-light-chain-enhancer of activated B Cells; NO•=nitric oxide; NOX=nicotinamide adenine dinucleotide phosphate-oxidase; Nrf2=nuclear factor erythroid 2; PTN=protein; Refs=references; RONS=reactive oxygen and nitrogen species; ROS=reactive oxygen species; SOD=superoxide dismutase. –= did not alter; * human study; #clinical studies, in human beings

reduced [88].

The recognition of ROS/RNS and redox-mediated protein modifications as transducing signals has opened up a new field in cell regulation and provided a novel way of controlling disease processes. Such approach has been proven feasible for gene expression governed by the transcription factor NF-κB [89]. This mediator is activated when membrane cell receptors, such as interleukin 1 beta (IL-1β), TNF receptor 1 (TNFR1), nicotinamide adenine dinucleotide phosphate-oxidase (NOX) and toll-like receptors type 4 (TLR4) promote the phosporylation of its NF-κB inactive form (IκBα). After entry into the nucleus, NF-κB stimulates pro-inflammatory, pro-oxidant and pro-apoptotic genes, for instance, COX2 (cyclooxygenase 2), iNOS, caspases and others [90].

Still in the field of transcription factors, another anti-inflammatory mediator, nuclear erythroid 2 factor (Nrf2), is emerging as an important OS biomarker. When activated for

antioxidant activity, in addition to inhibition of NF-κB, it causes attenuation of phosphorylated IκB and, in consequence, NF-κB degradation [91]. Nrf2 also stimulates activation of over two dozen genes involved in antioxidant and anti-inflammatory activities such as antioxidant response element (ARE), NAD(P)H quinone oxidoreductase-1 (NQO-1), heme oxygenase-1 (HO-1), peroxiredoxin 1, γ-glutamylcysteine ligase, GPx, and glutathione disulfide reductase [92]. Nrf2−/− mice had been used successfully in experimental model of colitis, confirming the closely role of this nuclear factor in bowel inflammation [93].

However, more recently, some results have brought doubts about the antioxidant and anti-inflammatory role of Nrf2. Kathiria et al. [94] identified an important effect of the prohibitin 1, a protein which regulates cell cycle progression, apoptosis, and transcription factor activity. It was shown to be decreased in mucosal biopsies from UC- and Crohn's disease-afflicted patients and in animal models of colitis. According to these authors, this protein maintained increased ARE activation and decreased intracellular ROS levels and increased colonic levels of the antioxidants HO-1 and NQO-1 via a mechanism independent of Nrf2. On the other side, [95] discovered a pro-oxidant action by Nrf2 via induction of transcription Kruppel-like factor 9 (Klf9) and further cell death.

Therefore, several agents, in special, dietary compounds, are used to modify or modulate molecular targets such as oxidative and or inflammatory markers, with the objective of prevention/amelioration of UC [37].

Thus, these results confirm the need for more investigations regarding redox profiles and markers in both states of health and disease. A summary of some biomarkers of OS found in this review is displayed in the Graphic Abstract.

3.3. Antioxidant therapy

When the antioxidant capacity of the damaged mucosa is compromised, the use of nontraditional therapy such as drugs, hormones, natural or synthetic substances and live organisms that eliminate RONS, inhibit cell damage (LP, protein and DNA modification) and improve the activity of antioxidant enzymes, can be beneficial, either associated or not with anti-inflammatory medicines [74]. Thus, agents that can target multiple molecular pathways, have fewer side effects, and are less expensive have enormous potential in the treatment of UC, with reduction of its severity, and in consequence, lead to a decrease in systemic damage [96].

3.3.1. Drugs, hormones, synthetic compounds and chemicals derived from sources other than vegetables

Pharmacological treatment of IBD attempts to minimize the symptoms associated with structural and functional abnormalities of the mucous membranes [23]. Current therapy includes corticosteroids and immunosuppressive agents (Fig. 2) and can cause serious adverse effects such as gastrointestinal problems (diarrhea, cramping, and abdominal pain), anemia, carcinogenesis, hepatotoxicity, nephrotoxicity and hypersensitivity reactions [97]. Another important observation refers to low or no response of some people to these medications [74].

3.3.1.1. Inhibitors of angiotensin II type 1. Among the studies evaluated in this review, the angiotensin II (Ang II) receptor antagonists (telmisartan and olmesartan – Fig. 2) have been shown to have beneficial outcomes (Table 1). These drugs act on angiotensin II type 1 (AT1) receptors, and as such, decrease angiotensin II action. This peptide promotes tissue inflammation through up-regulation/activation of NADPH oxidase with consequent generation of $O_2^{\bullet-}$ and causes activation of NF-kB, with sequential production

of pro-inflammatory cytokines, chemokines, growth factors, and adhesion molecules, which cause inflammation and fibrosis [98]. Among several candidates as Ang II receptor blockers (ARBs) such as valsartan and olmesartan, telmisartan (TLM) (Fig. 2) was the only one with anti-inflammatory and antioxidant characteristics. It blocks Ang II AT1 receptors and is a partial agonist of peroxisome proliferator-activated receptor-gamma (PPAR-γ), a nuclear transcription factor that plays a role in the regulation of carbohydrate and lipid metabolism, and suppresses inflammatory gene expression, with this effect being independent of the blood pressure-lowering effects induced by AT1 receptor antagonism, thus showing a marked protective effect on colitis [99].

According to Arab et al. [99], oral treatment with telmisartan (TLM) in rats (10 mg/kg bw/d for 1 week before induced colitis + 4 days after induced colitis) suppressed ROS generation by inhibition of NF-kB/p65, COX2 (cyclooxygenase type 2) and iNOS mRNA expression, as well as NF-kB/p65 protein colonic expression. Other antioxidant actions attributed to TLM were suppression of lipid peroxidation, scavenging of NO•, increasing of GSH levels, of total antioxidant capacity (TAC), and of SOD and GPx activity [99]. In a study by Guerra et al., they evaluated the use of TLM (1, 3, and 5 mg/kg bw/d) orally for 3 days before induction of UC in rats and also 2 and 24 h after induction, which showed that a dose of 5 mg/kg reduced colonic MPO activity and colonic levels of MDA [100]. These findings highlighted the beneficial effects of TLM for the treatment of IBD, which is mediated through modulation of colonic inflammation and OS (Table 1).

3.3.1.2. Inhibitors of hydroxymethylglutaryl COA reductases. The drug class called statins, in this review represented by simvastatin and rosuvastetin (Fig. 2), studied by Maheshwari et al. [101] presented an important antioxidant effect, represented by inhibition of MPO activity, decrease of lipid peroxidation and increase of SOD and GR activity in rats. The interest to test this class in UC is related to its anti-inflammatory and endothelial cell protective actions, independent of their antihyperlipidemic effects [102]. Besides attenuating OS, these drugs, especially simvastatin, also improve histologic parameters in TNBS-induced colitis in rats.

3.3.1.3. Hormones. Another nontraditional therapy, successfully tested on IBD, is hormone therapy, specifically melatonin (MEL) (Fig. 2). Chemically, MEL or N-acetyl-5-methoxytryptamine is a derivative of the essential amino acid tryptophan. In the gastrointestinal tract (GI), MEL comes from both pineal melatonin and de novo synthesis within the GI tract. It may have a direct effect on many GI tissues, serving as an endocrine, paracrine, or autocrine hormone, influencing the regeneration and function of epithelium, modulating the immune milieu in the gut, and reducing GI muscle tonus by targeting smooth muscle cells [103]. There is a large body of evidence depicting the protective effect of MEL in various experimental and clinical conditions [104]. It plays an important role as a regulator of inflammation, as well as in proper immune system and antioxidant system function for intestinal disorders [105]. In animal experiments, MEL administration was shown to have anti-inflammatory action through inhibition of IL-10, IFN-γ, TNF-α, IL-6, and NO•. As such, MEL also shows antioxidant properties such as free-radical scavenging; reduction of HO•, ONOO⁻, RO₂• and singlet oxygen levels [106]; inhibition of COX2 expression and NF-kB activation [107] and iNOS expression [108]; and increase of Nrf2 (nuclear factor erythroid 2) expression [104], which is a nuclear mediator for anti-inflammatory and antioxidant genes. All these results suggest that MEL may exert benefits on UC by reducing or controlling inflammation and OS. According to Tahan et al. [109], 100 mg/kg.bw/d MEL i.p. for 3 days in mice, decreased ROS synthesis, by inhibition of colonic MPO activity, as well as RONS damage by decrease of MDA colonic levels. In this study,

MEL also ameliorated antioxidant defenses by increasing colonic GSH levels and colonic SOD activity. In a study using mice conducted by Trivedi et al., a lower dose of MEL was tested: 1 mg/kg. bw/d MEL for 8 and 18 weeks, after colitis induction by dextran sulfate sodium (DSS). This treatment caused a significant decrease in the levels of inflammatory and oxidative colonic markers: MPO activity, COX2, signal transducer and activator of transcription 3 (STAT3) and NF-kB colonic expression, TBARS colonic levels and DNA damage [104].

Changes in MEL metabolism was also observed in patients with UC. These changes are related to the severity of the disease, and according to [110], adjuvant MEL therapy may help in sustaining remission in patients with UC. Although none of these studies has evaluated OS, the potential benefit of MEL is clear. New trials to analyze the antioxidant effect of MEL are needed.

3.3.1.4. Synthetic substances. A synthetic substance (pro-drug) with various antioxidant effects on colitis is N-acetylcysteine or NAC (Fig. 2). It acts as a cysteine prodrug and a GSH precursor [111]. Being a thiol (R-SH), it can be oxidized by various radicals and also serve as a nucleophile [111]. NAC is an artificial antioxidant that has shown positive results in both IBD animal models [112] and clinical trials [113], in addition to being used with success in the treatment of several disorders, such as intoxication [111], cardiac ischemia-reperfusion [114], chronic obstructive pulmonary disease (COPD) [115], bronchitis [116], HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome) [117], psychiatric disorders [118] and diabetes [119].

Antioxidant capacity reduction in a cellular environment is mainly due to a decrease of GSH and/or increased oxidized glutathione (GSSG) [116]. GSH depletion has been observed in both IBD patients and different models of colitis induction [120]. NAC increases antioxidant defense activity by providing cysteine, which is required for GSH synthesis. Furthermore, NAC decreases OS by RONS ($HO^\bullet$, $NO_2^\bullet$) scavenging, along with carbonate radical ($CO_3^{\bullet-}$) [111] and metal chelation (Cu^{+2}, Fe^{+3}, Cd^{2+}, Hg^{2+} and Pb^{2+}) which are metals involved in ROS generation and in the inflammatory response [121].

The anti-inflammatory and antioxidant activities of NAC have also been confirmed through observation of NF-kB inhibition [89]. This antioxidant activity may contribute to the therapeutic effects of NAC on IBD. According to [120], oral NAC (150 mg/kg bw/d) for 45 days along with 3 DSS cycles, generated a moderate impact on colonic oxidation of lipids and proteins, decreased colonic MPO and $NO^\bullet$ serum levels, and improved colon antioxidant status by increasing GSH and CAT activities, suggesting that a long term NAC diet might be beneficial for IBD.

Within the category "synthetic antioxidants and chemicals derived from sources, other than vegetables", we found substances naturally produced by human body or other non-probiotic alive organisms. Here, it stands the real therapeutic possibility of modified SOD and propionyl-L-carnitine (PLC) (Fig. 2), both already in clinical trial phase due to their high therapeutic power, however in this review, during the search period, there was no evaluation of OS markers (Table 1).

Due to its significant ROS scavenging ability, great interest has been focused on SOD, for therapeutic use. However, because of extremely rapid plasma clearance time, instability, and immunogenicity in vivo, the clinical application of SOD as a therapeutic agent has been very limited [122]. Several attempts to obtain active and stable SOD have been tested successfully in lung inflammation [123] as well as for IBD treatment. Inshihara et al. utilized a lecithinized human Cu/Zn–SOD (PC–SOD), in which four phosphatidylcholine-derived molecules were covalently bound to each SOD dimer. These authors observed, using inflammatory markers, that PC–SOD, administered intravenously (*i.v.*), decreased both MPO activity and phospho-NF-κB p65 [124]. In fact, administration of PC–SOD (40 mg/kg/d) for 14 days, had shown a safe and beneficial effect on UC-Disease Activity Index (DAI) [125].

Another modified SOD applied to IBD treatment was *Lactobacillus fermentum,* a recombinant superoxide dismutase (rec-SOD). This rec-SOD was able to improve redox imbalance by increasing oxidative defense (SOD colonic activity), decreasing ROS damage (LP) and as noted by [124] using PC–SOD, rec-SOD also reduced MPO, as well as NF-κB p65 expression in the colonic tissue [126], both in animal models.

Propionyl-*L*-carnitine (PLC), a natural ester derivative of *L*-carnitine that acts as an antioxidant molecule, is reduced in the serum of UC patients, suggesting that this molecule can serve as a source of *L*-carnitine, which plays an essential role in energy metabolism, since it transports activated long-chain fatty acids into the mitochondrial matrix, for β-oxidation [126]. In a phase II trial, PLC caused decreased symptoms (pain and rectal bleeding) in UC patients, compared to a placebo group [127]. Unfortunately, this multicentric trial did not investigate OS markers, and for that, they are not in our review. But it is possible to infer that, as identified by Scioli et al. [128], PLC can be an important scavenger and synthesis inhibitor of ROS, since classic IBD symptons have OS involved in the pathogenic process. These studies using experimental models and further studies in patients with UC contribute to a fundamental basis for its clinical use as a safe therapeutic alternative, but determination of safe doses and long-term studies are still necessary to ensure its correct prescription by health professionals.

3.3.2. Polyphenols and other natural active compounds of medicinal plants

Polyphenols or phenolic compounds refer to a broad group of molecules found mainly in plants that are characterized by the presence of one or more phenyl rings and one or more hydroxyl groups linked directly to the aromatic rings. They can be classified into five structural groups: phenolic acids, flavonoids, anthocyanins, stilbenes and lignans. A growing body of evidence indicates that polyphenols are health-promoting phytochemicals [129]. They possess antioxidant properties, acting directly as free-radical scavengers or indirectly by interfering with specific proteins in the redox signaling pathways that are involved in different biological functions [33].

Pure polyphenol standards can interfere with the induction of NF-kB and MAPKs signaling pathways in intestinal cells. Most of the studied polyphenols exhibited anti-inflammatory behavior by inhibiting the activation of the NF-kB cascade [130]. Furthermore, some polyphenols have been shown to have other functions, specifically in relation to the intestinal barrier (Table 1). In a study by Shigeshiro et al. [131], on experimental colitis, the administration of polyphenols: curcumin, quercetin, naringenin or hesperetin led, collectively, to restoring DSS-induced colitis, at least in part, through regulation of the colonic and tight junction (TJ) barriers. As described in the legend of Fig. 4, intercellular junctions are one of the mechanisms that provide intestinal integrity and RONS can promote disruption of these structures, by increasing intestinal permeability with neutrophil and bacterial/toxin infiltration, and by the inflammatory process [46,132]. Although Shigeshiro et al. [131] did not demonstrate a direct relationship between the use of polyphenols and OS, it is understood that these components may reduce the harmful action of ROS on the intestinal mucosa.

3.3.2.1. Resveratrol. Among the polyphenols, one of the most extensive and commonly studied is the resveratrol-based class (Fig. 2). These compounds are widely distributed in all foods of plant origin such as red grapes, in certain berries, and in peanuts. A

limiting factor for the use of resveratrol in the treatment of IBD is its low bioavailability, due to its rapid absorption and metabolism in the extensive upper gastrointestinal tract and liver. In order to improve its use for the treatment of this disease, a resveratrol-colon-specific drug delivery system was designed to overcome its poor solubility, limited stability, high metabolization in the upper gastrointestinal tract with increased efficacy, restoring enzymatic and nonenzymatic antioxidant defense, and decreased adverse effects [133,134]. However, one of the 41 papers found is a pilot study [135], which observed important antioxidant and anti-inflammatory effects on the activity of plasmatic NF-κB, confirming that this polyphenol is able to attenuate UC activity and may act, also, as an anticancer agent [136].

Abdin investigated the use of a colon-specific delivery of resveratrol in rats with colitis and observed a decrease in colonic MPO activity [137]. Similar results were observed for *trans*-resveratrol in studies by Larrosa et al. [138] and Yao et al. [139]. In addition, [140] reported additional antioxidant and anti-inflammatory effects of *trans*-resveratrol as observed by decreased COX1 and COX2 enzymes. Other markers for OS were improved after resveratrol use, such as decrease of colonic expression of iNOS and NF-kB in addition to MDA and colonic MPO levels [141–143].

Despite these promising results, the resveratrol dosage capable of maximizing health benefits without raising toxicity problems remains an area of controversial debate [144]. In fact, several studies have demonstrated that resveratrol can have a potent non-specific toxicity toward normal cells, particularly endothelial cells with a low oxidative condition. Resveratrol, in high concentration, had been recognized as a dangerous compound rather than as an antioxidant, by its metabolization through anti-xenobiotic enzymes, thus producing ROS [145]. As such, this evidence confirms the necessity for determining optimal doses of resveratrol to maintain the health of individuals.

3.3.2.2. Curcumin. Curcumin (Fig. 2), a hydrophobic polyphenol, is the major representative of curcuminoids, the main chemical constituents of the spice turmeric, and in curry powder. Turmeric is prepared from the root of the plant *Curcuma longa*, a member of the ginger family. It is native to India and Southeast Asia and has been used to treat a broad range of common ailments, especially inflammatory diseases, as an oral and topical medicine, in Indian Ayurvedic medicine for at least 4000 years, as well as in Chinese, Arabic and other traditional medicines [146]. Its beneficial effects on IBD were observed in animal models [147], through *in vitro* assays [148] and clinical trials [149,150]. The main effects attributed to curcumin are related to anti-inflammatory and anticancer activities [136], however in analyzing Table 1, we can observe that curcumin, alone [151,152], or in combination with other plants such as *Gingko biloba* [153] or compounds like aminoguanidine [154], show important antioxidant effects, like decrease of LP, and of RONS production, as well as increase of antioxidant enzymes. These results confirm that curcumin is a potential new treatment for IBD.

3.3.2.3. Quercetin. Quercetin (Fig. 2) was able to prevent oxidative injury and cell death by various mechanisms, for instance, as a ROS scavenger, an iron chelator [155] and an endogenous antioxidant (GSH) modulator [156]. It has been reported that quercetin plays an important role in cell cycle kinetics and proliferation and induction of apoptosis in cell culture [157]. Quercetin antioxidant capacity includes the most potent ROS, among them $O_2^{\bullet-}$, $HO^{\bullet}$, $RO_2^{\bullet}$, $RO^{\bullet}$, and reactive nitrogen species like $NO^{\bullet}$ and $ONOO^-$. According to its properties, [155] tested different orally administered doses (50 and 100 mg/kg.bw/d) for 10 days in TNBS (trinitrobenzene sulfonic acid)-colitis. In this study, both therapeutic

doses significantly attenuated colonic MPO activity, MDA levels and serum $NO^{\bullet}$ levels, while increasing the colonic levels of GSH. [156] evaluated the therapeutic effect and mechanisms of orally administered quercetin in microcapsules (100 mg/kg bw/d) on acetic acid-induced colitis. This microencapsulated form reduced MPO, increased GSH colon levels and presented an elevated antioxidant capacity evaluated through FRAP (Ferric Reducing Antioxidant Power).

In addition to their direct antioxidant action, some polyphenols, like quercetin, act in maintaining the intestinal barrier function by selective protein kinase C δ (PKCδ) inhibition, resulting in the promotion of occludin phosphorylation of TJ (tight junctions) assembly [158]. Although the precise mechanism underlying the quercetin mediated promotion of TJ protein assembly and expression remains unsolved, it is clear that this flavonoid induced the phosphorylation of occludin in human cell cultures concomitantly with the assembly of the TJs [159].

3.3.2.4. Catechin class. Another important polyphenols derived from the green tea, especially in the (−)-*epi*-gallocatechin-3-gallate (EGCG) fraction (Fig. 2), which represents up to 30% of the dry weight of green tea leaves [160]. Green tea is one of the most popular beverages consumed worldwide, being second, next to water. Although green tea consists of > 2000 components, interest has focused on the polyphenols which include EGCG, (−)-*epi*-gallocatechin (EGC), (−)-*epi*-catechin gallate (ECG) and (−)-*epi*-catechin (EC) (Fig. 2), all of which have potent antioxidant properties [161].

In order to improve bioavailability, stability, and cancer preventive activities of EGCG, per-acetylated EGCG (AcEGCG) was synthesized by [162] and tested in colitis by [163]. According to these authors, dietary consumption of AcEGCG demonstrated to be more effective than EGCG in preventing DSS-induced colitis. The antioxidant action of EGCC can be explained by several mechanisms, including activation of Nrf2 signaling. Despite this, none of the studies evaluated the effect of EGCG on enzymatic expression or activity. EGCG, like quercetin, improved intestinal TJ barrier dysfunction. However, the molecular mechanisms underlying these EGCG-mediated effects remain unclear [131].

Three papers evaluated the effect of grape seed proanthocyanidines (GSPs) on induced UC. GSPs contain approximately 89% proanthocyanidins, with dimers (6.6%), trimers (5.0%), tetramers (2.9%) and oligomers (74.8%) [164]. The antiproliferative, antioxidant, and anticarcinogenic effects of GSPs can be explained, principally, by their action on decreasing expression of NF-κB targeted genes [85,165,166]. According to Ref. [165], it is possible to consider that GSPs suppress IκK (inhibitor of κB kinase) activation, and the inactivated IκK complex suppresses the phosphorylation-induced degradation of IκBα (IκB kinase α). GSPs were also able to increase colonic SOD activity [85,166], confirming their antioxidant effect on improving enzymatic defense.

3.3.2.5. Others. Myricetin, narigenin, kolaviron and amentoflavone (Fig. 2) were also successfully, used for IBD (animal model). These substances were tested by oral [167–169] or *i.p.* [83] administration. Independently of routes, most flavonoids exhibited free radical scavenger ability, particularly toward $NO^{\bullet}$ [155,170–172], reduced lipid peroxidation [83,155,170–172], promoted an increase in antioxidant defense, principally through SOD activity [83,155,170–172] and GSH levels [83,155,156,171]. In analyzing these results, the potential therapeutic use of flavonoids becomes evident. However, it should be pointed out that they concurrently have pro-oxidative properties, which have some associations with potential toxicity [173]. Furthermore, because this antioxidant power has only been tested in animal models, clinical trials are necessary to determine the flavonoid efficacy not only in the acute

IBD phase, but also in the remission phase, in order to promote a better quality of life for IBD patients.

Other natural substances with antioxidant power had been identified in plants. A recent meta-analysis carried out on herbal therapy in humans concluded that herbal medicines may safely induce clinical response and remission in patients with IBD (histological index and adverse event) [174], however no parameter observed was related to OS. Furthermore, neither extract nor natural compound has been so far recommended by the International Society of Nutritional Therapy as adjuvant therapy for IBD [175,176].

In this review, 21 active compounds were identified and tested in IBD therapy (Table 1), all of them in animal models. The pigment indicaxanthin (Fig. 2) [177], which antioxidant activity *in vitro,* involves reduction of the expression of COX-2 and iNOS associated to inhibition of NF-κB activation, and consequently inhibition of RONS synthesis and scavenging of NO$^\bullet$ and ROS, stands out. The alkaloid berberine [178] obtained from the rhizome of *Coptidis japonica* and the stem bark of *Mahonia aquifolium,* which antioxidant action in TNBS-induced experimental colitis involves reduction of RONS synthesis (decreasing expression of COX2 and iNOS and MPO activity) plus decrease of MDA levels, stimulation of SOD and CAT activities and increase of GSH content is also noticeable. The active compounds of *Cannabis sativa,* cannabigerol [179] and cannabidiol [180] (Fig. 2), which present non-psychothropic actions and in face of their antioxidant activities such as scavenger of RONS and decrease of iNOS expression, may stimulate future studies.

Despite different alterations identified for antioxidant defense, the active compounds utilized in IBD treatment were able to improve redox imbalance, reducing the levels or activity of OS when the antioxidant was increased and *vice versa.*

Thus, identification and characterization of novel anti-inflammatory and antioxidant components of plants may aid in improving current nutritional formulas. In face of this evidence, it is feasible to assert that herbal therapy shows beneficial results for both inflammation and OS, in animal models.

3.3.3. Functional foods, antioxidant nutrients and probiotics

The impact of functional foods on the course of IBD has been examined for a small number of specific dietary factors (Table 1) [181].

3.3.3.1. Camel's milk.
Camel's milk (CM) might represent a potential candidate for pharmacological efficacy on IBD with minimal adverse reactions [31]. It is different from other ruminant milk, due to its high content in minerals (calcium, iron, magnesium, copper and zinc), vitamins (A, B2, C and E) and insulin, and lower content in fat, cholesterol, protein and sugar [182]. It also contains a relatively large amount of polyunsaturated fatty and linoleic acids, which are essential for human nutrition [183]. With regard to the high risk of malnutrition in the course of IBD, nutritional support plays a crucial role in the management of these patients. CM has been consumed as an essential nutritional supplement with high energy and vitamin content to help immune-deficient patients [31]. Malabsorption syndrome has been identified as potential trigger for symptoms of IBD, such as abdominal pain, bloating and distension, altered bowel habits and malnutrition [184,185].

Besides having antioxidant properties, CM is rich in lactoferrin, a protein with marked antioxidant and anti-inflammatory properties [186]. In view of these properties, Arab et al. evaluated the effects of CM (10 mL/kg.bw/d by gavage, one week before colitis induction (*c.i.*) and at the 4th day post *c.i.*) against TNBS-induced colitis in rats. Attenuation of colon injury was observed through suppression of OS via reduction of lipid peroxides (MDA), NO$^\bullet$ and

MPO activity along with boosting of the antioxidant defenses through restoration of colonic GSH and total antioxidant capacity (TAC) [31].

More studies are necessary to investigate if CM may be a valuable complementary approach for the management of IBD.

3.3.3.2. Extra virgin olive oil.
Another functional food that may exhibit beneficial effects on IBD without undesirable effects that accompany the classical pharmacotherapy is extra virgin olive oil (EVOO) [187]. It is a typical ingredient in a Mediterranean diet. It is obtained from the fruit of the olive tree solely by mechanical or other physical means under conditions that do not lead to alteration of the oil [188]. EVOO could modulate responses against OS, for all antioxidant enzymes and consequently attenuate IBD [189]. EVOO consumption increases the activity of antioxidant enzymes such as CAT, SOD and GPX [190]. The protective role of EVOO is the result of its specific composition including high proportions of mono-unsaturated fatty acids (oleic acid), a balanced presence of poly-unsaturated fatty acids and other minor components, such as α-tocopherol and phenolic compounds [191], such as simple phenols (hydroxytyrosol, tyrosol), aldehydic secoiridoids, flavonoids and lignans (acetoxypinoresinol, pinoresinol) [187].

Previous studies have shown that patients with IBD are among the highest risk groups for developing colon-rectal cancer (CRC) [192]. Experimental studies have indicated a role of dietary lipids on cancer, particularly in colon tumor development. For instance, it was demonstrated that high fat diets rich in ω-6 poly-unsaturated fatty acids and saturated fatty acids promote carcinogenesis, while high fat diets rich in ω-3 fatty acids had a protective effect [193,194]. Considering that chronic inflammation is the key predisposing factor to CRC in IBD, [195] evaluated an EVOO diet (5%) in DSS-induced colitis for 5 weeks. In these animals, suppression of COX2 and iNOS colonic expressions was observed. COX2 is expressed in response to growth factors (transforming growth factor α), pro-inflammatory cytokines (interleukin 1α) [196], while iNOS produces large amounts of NO$^\bullet$ which is implicated in initiation, promotion and progression of tumors [197]. This study indicates that chronic feeding of a 5% olive oil diet for 5 weeks attenuates inflammation in DSS-induced colitis of rat colons, based on evaluations using COX2 and iNOS [195].

As already shown, phenolic compounds are recognized as holders of important antioxidant, anti-inflammatory, anti-microbial, antiproliferative, antiarrhythmic, platelet antiaggregant and vasodilatory effects, as well as able to modulate important cellular signaling pathways [188,198]. EVOO has remarkable antioxidant potential derived from its high level of phenolic compounds [189]. Sánchez-Fidalgo et al. [199] investigated the effects of an EVOO diet enriched with its principal polyphenols-hydroxytyrosyl acetate (HTy-Ac) and 3,4-dihydroxyphenylglycol (DHPG) (Fig. 2) (both at 0.1% for 30 d before *c.i.*) on the severity of DSS-induced acute inflammation. Only the HTy-Ac supplemented group showed a reduction in COX2 and iNOS colonic protein expression. Furthermore, in DSS-treated mice, supplemental HTy-Ac blocked the activation of the NF-kB pathway and boosted antioxidant defenses through the decrease of MPO colonic activity, and reduction of the degree of polymorphonuclear neutrophils infiltration [199].

Given the few experimental studies performed, addressing the protective activity of olive oil on colon cancer and the anti-inflammatory and antioxidant properties of the compounds present in EVOO, further experimental and clinical studies are needed to investigate whether olive oil intake and its doses are effective to attenuate OS and inflammation in UC.

3.3.3.3. Micronutrients.
Some micronutrients found in food, such as α-tocopherol or vitamin E and ascorbic acid (vitamin C), act as

exogenous antioxidant defenses. For this reason, food rich in antioxidants or antioxidants administered as supplements are applied on a large scale in an attempt to alleviate ROS induced damage such as apoptosis, alteration in immune response modulation and innate immunity, and others [200].

Vitamin E is the blanket term that covers all biologically active tocopherols and tocotrienols and their derivatives. Numerous beneficial health effects have been proposed for vitamin E, which are attributed to its antioxidant activity [201]. Additionally, vitamin E is associated with a reduced risk of coronary heart disease [202] and colon cancer [203].

Chemically, vitamin E is a lipid-soluble vitamin, which is biologically active in tissues and plasma. Tocopherols, therefore, protect lipid membranes by quenching/scavenging singlet oxygen (and potentially also other ROS, such as HO$^\bullet$) [204]. Despite the beneficial action of vitamin C, which can contribute to vitamin E regeneration [205], in vivo studies have demonstrated contradictory results when this vitamin is combined with other antioxidants. According to [206], vitamin E, vitamin C and lipoic acid protect the arachidonic acid level in the brains of diabetic and non-diabetic rats. However, when a combination of high doses of vitamin E with oxidized sunflower oil is used, this vitamin presents pro-oxidant action [207].

The major impediment to vitamin E use in the treatment of acute inflammatory diseases such as UC, is its low solubility in water, preventing its oral ingestion or enema administration in patients. Therefore, the use of derivatives of vitamin E such as tocopheryl acetate and α-tocopheryl phosphate, which are more water soluble [208], have been preferred as dietary supplements.

α-Tocopherol was utilized alone [47] and in combination with other nutrients [209,210]. Interestingly, the results had shown an absence of colonic antioxidant effect, when vitamin E was utilized with vitamin C and GSH [210]. Some meta-analyses have shown that antioxidant supplements do not result in the presumed health benefit, but paradoxically a high intake of antioxidants is associated with increased mortality [211,212]. Those observations suggest a pro-oxidant effect of antioxidants and it seems that this deleterious effect is associated to Nrf2 mutations [213].

Other nutrients relevant to the maintenance of intestinal homeostasis are selenium (Se) and zinc (Zn), essential elements for the restructuring of antioxidant enzymes such as GPx and SOD. Selenium interacts with the active site of GPx, which is essential to combat ROS and to regenerate adipocytes by reacylation. On the other hand, zinc as a SOD cofactor is indirectly involved with oxidant defense. When this mineral was used in combination with vitamin E [209] or anti-TNF-α (a drug preconized for the treatment of CD) [214], an improved redox balance was observed in plasma and/or colonic tissue (Table 1).

Aghdassi et al., in 2003 [215], conduced the first randomized controlled trial on antioxidant (Vitamins C and E) on CD. These authors observed an important decreased of oxidative damage (reduction of LP in plasma) in patients, which received the supplementation for 4 weeks, versus placebo group. More recently, in 2008, Roggenbuck et al. [216] studied six patients with CD which received a nutritional formulation containing several antioxidants (Vitamin C, vitamin E, β-carotene, zinc, selenium and glutamine) for 4 weeks. According to those authors, this supplementation was not sufficient to improve oxidative stress and inflammatory biomarkers, but increased antioxidant status of plasma and inflamed mucosa. Thereby, they concluded that supplementation was inconclusive and stimulated to continuation this therapeutic approach in placebo-controlled trials.

From these results, it is fundamental before prescribing antioxidant nutrients, to understand that each antioxidant has its own unique biochemical profile and therefore antioxidants should not be treated as a group [201].

Recently, an interesting review conducted by Di Stasi and Costa [217] evaluated patent literature focused on chemical compounds, functional foods and biological therapy useful for the treatment of IBD. The paper selected 33 patented products during the period 2013–2014 and just one of them was included in this review, lipoic acid. However, the authors were critical about the quality of those patents, once most of them are not conclusive because they were based on data from unspecific methods that are not related to intestinal inflammation. Besides that, clinical studies have rarely been described in patients, strongly limiting their evaluation and medical applicability.

3.3.3.4. Probiotics. In recent years, a rising interest in the hypothesis that gut dysbiosis can result in immune impairment effects associated with IBD, resulted in several studies on probiotics and prebiotics. Probiotic bacteria may be defined as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host [169].

The antioxidant action of probiotics can be due to ROS scavenging, metal ion chelation, enzyme inhibition, and the reduction and inhibition of the ascorbate autoxidation [218,219], as well as the synthesis of antioxidant enzymes by bacteria used in the formulas [220]. Probiotic antioxidant power had been demonstrated in healthy subjects by increased Total Antioxidant Activity – TAA – and Total Antioxidant Status – TAS [221], in cardiovascular disease, by decreased ROS production [222], and in non-alcoholic fatty liver disease in children, as shown in a review by Yang et al. [223].

In a recent in vitro and in vivo study, using Lactobacillus and Bifidobacterium conducted by Amaretti et al., the authors identified that given the colon colonization by administered probiotics, it is conceivable that their overall protective effect could be related to activities taking place at the intestinal level, i.e., secretion of enzymes like SOD, metal-chelating activities, promotion of the production of antioxidant biomolecules such as exopolysaccharides that had shown in vitro antioxidant and free-radical scavenging activities [224].

Even it a specific pathogen has not yet been identified as an etiopathogenetic factor and a definite infectious cause cannot be considered alone, the involvement of gut microbiota in the pathogenesis of these diseases is generally recognized [225]. Several studies in UC patients have demonstrated anti-inflammatory effects and improvement of clinical markers as a result of probiotics use, in particular E. coli Nissle 1917, VSL#3, Lactobacilli and/or Bifidobacteria [169]. However, for CD, there have been no benefits that would recommend their use [226].

Although few studies (Table 1), and all in animal models, have investigated antioxidant action by probiotics, these microorganisms have been shown to increase SOD, CAT and GPx activity [220,227], GSH levels [227], as well as to reduce MPO [228] and NO$^\bullet$ [229] activity. However, a noticeable result was reported by Gardlik et al., who used recombinant probiotics. According to these authors, despite the lack of increase in MDA levels and advanced oxidation protein products in colitis induced by the DSS group, administration of all E. coli strains lowered these parameters, when compared to the control group [230].

This result suggests a potential antioxidant action caused by probiotics and the daily use of 200 mg of E. coli Nissle 1917 (Mutaflor) may be an option for UC patients who are unable or unwilling to take mesalazine, as recognized by the British Society of Gastroenterology [231]. However, one of the difficulties found in this review, regarding this nutraceutical, was the diversity of bacterial strains and therapeutic doses used.

Jonkers et al. conducted a systematic review about probiotics in management of IBD and concluded that future studies should focus on specific disease subtypes and disease location [232].

Besides, it is fundamental to investigate further all therapeutical possibilities of probiotics for IBD, including their antioxidant power.

4. Conclusions and future perspectives

Alternative therapies for IBD are a vast field of scientific interest. In this systematic review, 101 different substances/live organisms/functional foods with antioxidant capacity, principally for UC, were identified. However, few compounds were tested more than once, including: the angiotensin II receptor antagonist [99,100,233]; the inhibitors of hydroxymethylglutaryl COA reductases [101]; the hormone MEL [96,103,109,234]; the synthetic substances N-acetylcysteine [120,235–238], bis(1-hydroxy-2,2,6,6-tetramethyl-4-piperidinyl)decandioate [239,240] and 3,4-oxo-iso-propylidene-shikimic acid [241–243]; resveratrol, some of its derivatives [137,138,140–143,244] and curcumin [151–154]; the flavonoids proanthocyanidin from grape seeds [85,165,166]; quercetin [155,156]; coumarin derivatives [76,245,246]; the microalga spirulina [247,248]; active compounds such as cannabigerol [179] and cannabidiol [180] from *Cannabis sativa* [179,180], which hampered the performance of a meta-analysis.

Several OS biomarkers were employed in all the papers, in particular: NO$^{\bullet}$, the pro-oxidant enzymes MPO and COX2, the transcriptor factor NF-kB; antioxidant enzymes SOD, CAT, GPx and the non-enzymatic antioxidant compound GSH or the ratio GSH/GSSG. This chemical diversity contributes to the understanding of the metabolic pathways. However, only few studies analyzed Nrf2 expression [11,55,96,104] and, in view of its strong association with redox imbalance and inflammation, as discussed previously, the regulation of Nrf2-ARE signaling may be closely linked with pharmacological intervention. Thus, the knowledge of the mechanism and consequent control of these redox-dependent events where the tested substances are used can provide us with alternatives to attenuate inflammatory-mediated diseases at the molecular and metabolic level.

Besides the role of OS in IBD etiology, the consistent increase of RONS have an important action in the recurrence of the active phase (Fig. 1) and consequently the use of antioxidants may help in the maintenance of remission phase [36].

According to Piganelli & Delmastro (2011), optimal treatments may have to incorporate antioxidants together with anti-inflammatory agents, such as NFκB activation inhibitors, and must also take into consideration the limitations associated with the use of intact enzyme/protein therapies, such as bioavailability, immunogenicity-limited cellular accessibility, and the cost of production [249]. In this context, functional foods and natural active compounds of plants fit very well for the treatment of IBD

In vitro and *in vivo* preclinical models, like the ones cited in the review, are fundamental to confidently test several isolated compounds/extracts/nutraceuticals/hormones/foods, before human trials. This fact partially explains why only two papers, based on the criteria adopted (OS markers), reported the use of compounds in humans subjects: resveratrol [135], extract pycnogenol in children [250] and antioxidant nutrients [215,216]. Others were performed and included in the present review, but could not enrich the statistics, once OS markers were not assessed.

It is clear that more research is necessary in order to implement the use of these compounds/drug/foods/synthetic substances, thus paving the way for new therapeutic possibilities to be brought to millions of IBD patients. Studies regarding pharmacokinetic parameters and metabolic profiles are essential and are normally the first approach in clinical trials [311].

It is essential that the same substance is tested several times in various conditions (acute, chronic, recidive, and CHC) and in different models before being tested in humans.

It is strongly desirable that research on IBD and their etiology or triggering factors in humans involves OS markers, because it is clear that this phenomenon is crucial to the onset of inflammation and that this, in turn, is directly related to the aggravation of the disease, by a concomitant formation of RONS. Until these issues are fully understood, in the fundamental and molecular levels, in terms of pharmacokinetics and metabolism, health professionals should assess individually the prescription of these substances/ natural or synthetic compounds is valid for their patients with IBD. However, actually, in face of all results, the alternative antioxidant therapy to IBD seems promising and must be further and continuously investigated, especially, in clinical trials.

Acknowledgments

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