NUTRITION RESEARCH 32 (2012) 801–816

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.nrjournal.com

Review of natural products actions on cytokines in inflammatory bowel disease

Sun Jin Hur[a], *Sung Ho Kang*[b], *Ho Sung Jung*[b], *Sang Chul Kim*[b], *Hyun Soo Jeon*[b], *Ick Hee Kim*[b], *Jae Dong Lee*[b,*]

[a] *Department of Molecular Biotechnology, Konkuk University, Seoul, Korea*
[b] *Department of Medicine, School of Medicine, Konkuk University, Chungju, Chungbuk, Korea*

ARTICLE INFO

Article history:
Received 4 December 2011
Revised 7 May 2012
Accepted 24 September 2012

Keywords:
Inflammatory bowel disease
Natural products
Cytokine
Phytochemicals
Probiotics

ABSTRACT

The purpose of this review is to provide an overview of the effects that natural products have on inflammatory bowel disease (IBD) and to provide insight into the relationship between these natural products and cytokines modulation. More than 100 studies from the past 10 years were reviewed herein on the therapeutic approaches for treating IBD. The natural products having anti-IBD actions included phytochemicals, antioxidants, microorganisms, dietary fibers, and lipids. The literature revealed that many of these natural products exert anti-IBD activity by altering cytokine production. Specifically, phytochemicals such as polyphenols or flavonoids are the most abundant, naturally occurring anti-IBD substances. The anti-IBD effects of lipids were primarily related to the n-3 polyunsaturated fatty acids. The anti-IBD effects of phytochemicals were associated with modulating the levels of tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, inducible nitric oxide synthase, and myeloperoxide. The anti-IBD effects of dietary fiber were mainly mediated via peroxisome proliferator–activated receptor-γ, TNF-α, nitric oxide, and IL-2, whereas the anti-IBD effects of lactic acid bacteria were reported to influence interferon-γ, IL-6, IL-12, TNF-α, and nuclear factor-κ light-chain enhancer of activated B cells. These results suggest that the anti-IBD effects exhibited by natural products are mainly caused by their ability to modulate cytokine production. However, the exact mechanism of action of natural products for IBD therapy is still unclear. Thus, future research is needed to examine the effect of these natural products on IBD and to determine which factors are most strongly correlated with reducing IBD or controlling the symptoms of IBD.

Abbreviations: 5-ASA, 5-aminosalicylic acid; CD, Crohn disease; CLA, conjugated linoleic acid; COX-2, cyclooxygenase-2; DHA, docosahexaenoic acid; DSS, dextran sulfate sodium; EGCG, epigallocatechin-3-gallate; EPA, eicosapentaenoic acid; HO-1, heme oxygenase-1; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MPO, myeloperoxide; NF-κB, nuclear factor-κ light-chain enhancer of activated B cells; NO, nitric oxide; PGE, prostaglandin E; PPAR-γ, peroxisome proliferator–activated receptor-γ; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.

* *Corresponding author: Department of Medicine, School of Medicine, Konkuk University, Chungju, Chungbuk 380-704, Korea Tel.*: +82 43 840 8210; fax: +82 43 843 6655.
E-mail address: jdongl@kku.ac.kr (J.D. Lee).

0271-5317/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nutres.2012.09.013

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn disease (CD) and ulcerative colitis (UC), represents a group of chronic disorders characterized by gastrointestinal tract inflammation [1,2]. The main causes of IBD are not well understood, but imbalances in proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interferon-γ, (IFN-γ), interleukin (IL)-1, IL-6, and IL-12 and anti-inflammatory cytokines including IL-4, IL-10, and IL-11 are thought to play a central role in mediating and modulating inflammation [3]. Inflammatory bowel disease therapies generally include anti-inflammatory or immunosuppressive drugs such as 5-aminosalicylic acid (5-ASA) and 6-mercaptopurine; however, most of these treatments are inadequate [4].

There is a clinical need to identify new and safe compounds for preventing or treating IBD [5]. Consequently, many patients turn to alternative strategies including traditional plant–based remedies [4]. In particular, phytochemicals are an important, naturally derived alternative therapy for IBD. García-Lafuente et al [6] suggest that phenolic compounds, as an alternative natural treatment, offer great hope for improving the symptoms of these diseases, but most studies on the anti-inflammatory effects of phenolic compounds have focused on immune or nonintestinal cells [7].

Numerous investigators reported that plant derivatives such as phenolic compounds and flavonoids exhibit anti-inflammatory activity by modulating the expression levels of various cytokines including IL-1, IL-6, IL-10, nuclear factor-κ light-chain enhancer of activated B cells (NF-κB), TNF-α, inducible nitric oxide (NO) synthase (iNOS), and cyclooxygenase (COX)-2. Moreover, many plant-derived extracts and chemicals have pharmacologic effects and clinical benefits. However, the claims that many natural medicines marketed to the general population are beneficial are often supported only by empirical or preliminary scientific data [8]. Therefore, the purposes of this review are to provide an overview of the effects of natural products on IBD and to present information regarding the relationship between these natural products and cytokine modulation.

2. Summary of the literature cited

Results of more than 100 studies published in the past 10 years related to the relationship between natural products and IBD are shown in Tables 1 and 2. The review included electronic searches of the PubMed, Medline, Scopus, and Google scholar database with the search terms as follows: “IBD therapy,” “natural products,” “phytochemicals,” “antioxidants,” “probiotics,” “fibers,” “cytokines,” and “extracts” in various combinations. Herein, a summary of literature on the relationship between cytokines and IBD and phytochemicals, antioxidants, microorganisms, dietary fibers, and lipids that display anti-IBD properties is presented. Moreover, the review summarizes the recent progress in determining the biological effects,

Table 1 – Active compounds in natural products and their target IBD-related factors

Active compounds \ Active factors	TNF-α	IL-6	iNOS	IL-1β	NO	NF-κB	MPO	IL-10	COX-2	IFN-γ	PGE_2	JNK	PPAR- γ	IL-12	IL-8	IL-2	IL-4
5-aminosalicylic acid	■	■	■	■		■	■						■				
Adenosine	■		■														
Anthraquinones	■																
Ascorbic acid	■	■			■			■		■							
Butyrate	■	■		■		■	■	■									
Carotenoids	■	■			■			■		■							
Catechin	■		■			■	■		■			■					
Chromone	■	■		■	■												
CLA	■	■		■		■							■	■			
Cordycepin	■		■														
DHA, EPA	■	■		■				■	■		■		■	■	■	■	
Ellagic acid			■						■		■						
Flavonoids	■	■	■	■	■				■		■	■					
Gallic acid			■														
Gingerols							■										
Glycoside	■	■				■											
Glycyrrhizin	■	■			■			■			■						
Isoflavone	■	■		■	■					■							
Kaempferol	■			■						■							
Kaurenoic acid							■										
Lactic acid bacteria	■	■	■			■		■	■	■				■	■		
Phenolic acid						■	■					■					
Polyphenols	■	■			■			■		■							
Polysaccharide	■		■														
Proanthocyanidins	■						■		■								
Procyanidins															■		■
Quercetin	■		■	■						■							
Rutin	■	■	■	■	■	■		■			■						
Shogaols							■										
Tannins	■		■				■		■			■					
Tearubigin		■	■		■	■					■	■					
Terpenoids	■	■	■		■	■			■			■					
Trucaprylin	■			■													

Table 2 – Effects of various phytochemicals on IBD

Products	Active compounds	Active factors	Reference
Plant-based materials			
A cochliacarpos extract	Tannins, Proanthocyanidins, Catechin	Decrease of MPO activity, diminish of TNF-α, reduction of COX-2, JNK and iNOS	[9]
Adlay bran fraction	Aurone, chromones, dihydrochalcone, chalcone, flavanones, flavones, isoflavone	Inhibited NO synthesis, suppressed LPS-stimulated IL-6 and TNF-α secretions	[10]
Almond skin powder	Flavonols, flavanones, and phenolic acid	Reduced MPO, NF-κB and p-JNK activation	[11]
Aloe	Anthraquinones, chromone	Decreased TNF-α, IL-1β mRNA expressions	[12]
Antioxidants	S-adenosylmethionine, a glutathione precursor, green tea polyphenol	Inhibition of NF-κB activation, improved hematocrit	[13]
Apple procyanidins	Procyanidins	Reduced IL-4 and IL-13, inhibited IL-8 expression	[14]
Apple polyphenols extract	Polyphenols	Increased COX-2, TNF-α, calpain, and tissue transglutaminase mRNA	[15]
Astragalus membranaceus extract	Kaempferol, quercetin, formononentin, calycosin, kumatakenin and Isoflavone glucosides	Diminished overexpression of TNF-α, IL-1β, and IFN-γ	[16]
Black tea polyphenols	Tearubigin	Reduced NO and O_2-associated with the favorable expression of T-helper 1 cytokines and iNOS, suppressed NF-κB	[17]
Bombax malabaricum extract	*B malabaricum* extract	Reduction of MPO, reduced TNF-α	[18]
Boswellia serrata extract and pure compound	(6*aR*,6*bS*,8*aR*,11*R*,12*S*,12*aR*,14*bS*)-1,2,4a,5,6,6*a*,7,8,8*a*, 9,10,11,12,12*a*-tetradecahydro-4,4,6*a*,6*b*,8*a*,11,12,12*a*,14*b*, nonamethyl picene-3, 14(4*H*,6*bH*,14*aH*,14*bH*)-dione (12-ursene 2-diketone) with a molecular weight of 438.691 g/mol, and the molecular formula is $C_{30}H_{46}O_2$	Inhibited NO, TNF-α, IL-1β, JNK	[19]
Chrysanthemum indicum extract	Flavonoids, terpenoids, phenolics	Inhibited NO, PGE_2, TNF-α, IL-1β production, mRNA and protein expression of iNOS and COX-2, attenuated the activation of JNK	[20]
Codium fragile extract	Flavonoids, β-carotene, tocopherol	Inhibited NO, PGE_2, TNF-α, decreased iNOS, COX-2	[21]
Copaifera langsdorffii	Kaurenoic acid	Reduced MPO, decreased MDA	[22]
Cordyceps militaris extract	Cordycepin, adenosine, polysaccharide	Suppressed epithelial damage, inhibited iNOS and TNF-α mRNA expression	[23]
Cyperus rotundus extract		Inhibition of NO production, suppression of iNOS mRNA and O_2^- expression	[24]
Eucalyptus globules leaf extract	Hydrolyzable tannins, gallic acid, ellagic acid, quercetin	Suppressed hepatic iNOS expression, inhibited iNOS induction, increased serum ALT and AST	[25]
Folium syringae leaves extract	Iridoid glycosides	Down-regulation of NF-κB p65, increase of mRNA expression of NF-κB p65	[26]
Ginger extract	Gingerols and shogaols	Reduction of MPO, decrease of malondialdehyde and protein carbonyl, inhibit cycloxygenase enzymes, suppression of colon MPO	[27]
Ginkgo biloba extract	Ginkgo-flavone glycosides, terpenoids	Reduced lipid oxidation, inhibition the protein and mRNA expressions of TNF-α, NF-κB p65 and IL-6	[28]

(*continued on next page*)

Table 2 (*continued*)

Products	Active compounds	Active factors	Reference
Green tea	EGCG	Reduced activation of NF-κB and AP-1	[29]
Kaempferol	Kaempferol	Decreased NO and PGE_2, decreased plasma LTB_4 level, suppressed colonic mucosa MPO activity	[30]
Kiwifruit extract	Ursolic acid, carotenoids, ascorbic acid, polyphenols	Decreased IFN-γ production, TNF-α and IL-10, reduced NO production, concentration of IL-6	[31]
P scabiosaefolia extract	Total phenol and flavonoids	Inhibition of mRNA expression of TNF-α, IL-1β, IL-6	[4]
Polygoni Rhizoma extract	Resveratrol and emodin-8-β-D-glucoside	Reduced IL-6, TNF-α, iNOS, NO, COX-2 and PGE_2, inhibited transcriptional activity of NF-κB	[32]
Polyherbal formulation (*Aegle marmeloes*, *C rotundus*, *Coriandrum sativum*, *Vetiveria zizanioides*)	Polyphenols, oil	Antibacterial and antifungal activity, carminative and stomachic actions	[33]
Polyphenolic extract (grape seed, cocoa, sugar cane, oak, mangosteen, pomegranate)	Phenolics	Sugar cane, oak and pomegranate inhibited NF-κB activity, pomegranate slightly inhibited Erk1/2 activation, pomegranate and cocoa decreased PGE_2 synthesis	[34]
Pomegranate extract	Vicenin-2, ferulic acid derivative, urolithin-C, urolithin-B, ellagic acid	Decrease iNOS, COX-2, PGE synthase, PGE_2, decrease oxidative stress, modulate favorably the gut microbiota	[35]
Porphyra dentate extract	Phenolic compounds (catechol, rutin, and hesperidin)	Inhibited the production of NO, suppression of up-regulation of iNOS promoter and NF-κB enhancer	[36]
Roasted licorice extracts	Glycyrrhizin, isoliquiritigenin, licochalcone, glabridin	Reduced NO and PGE_2 production, plasma TNF-α and IL-6, increased plasma IL-10 production	[37]
Rutin	Rutin	Attenuate the production of IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF) and iNOS	[38]
Soy	Soy-derived dipeptide and tripeptide	Decreased IFNG, IL-1β, TNF-α, IL-17 α and mMPO activity	[39]
Lipid-based materials			
CLA	CLA	Induction of colonic PPAR-γ and its responsive gene PPAR-γ–coactivator-1α and down-regulation of TNF-α	[40]
CLA	CLA	Enhanced PPAR-γ expression, repressed TNF-α expression and NF-κB p65 activation	[41]
CLA	CLA	Enhancing PPAR-γ activity	[42]
CLA	Cis-9,trans-11-CLA	Reduced TNF-α, IL-6 and IL-12 p35 mRNA levels, and IL-12p70 concentrations	[43]
CLA	9E,11E-CLA	Enhanced IL-1Ra, inhibited IL-1α, IL-1 and IL-6β	[44]
Dietary arachidonic acid	Arachidonic acid	Down-regulation of IL-8, IL-6	[9]
Fatty acid from fish	ω-3 fatty acids	Decreased serum IL-6 and TNF-α concentrations	[45]
Fish oil	DHA, EPA	Reduced IL-2 production, T_H1 and T_H2 cytokines, decreased TNF-α, IL-1β, IL-1β	[46]
Medium-chain triglycerides and n-3 fatty acids	Trucaprylin, soybean oil, palm oil, corn oil	Attenuated TNF-α, IL-1β	[47]
n-3 PUFA	EPA, DHA	Decreased VCAM-1, TLR4, COX-2, VEGFR2 expression, IL-6, IL-8 and GM-CSF, reduced production of PGE_2.	[48]
n-3 PUFA	DHA, EPA	Decreased arachidonic acid in the rafts	[49]
n-3–rich PUFAs	Linoleic acid, arachidonic acid, EPA or DHA	Decreased TNF-α, IL-1β, and IL-12	[50]
Nitrated oleic acid	9- or 10-nitro-octadecenoic oleic acid	Increased expression of PPAR-γ	[51]
Quercitrin, olive oil with fish oil, EPA, and DHA	Quercitrin, olive oil, EPA, and DHA	Quercitrin = inhibition of colonic TNF-α and IL-1β, antioxidant activity; fish oil = inhibition of colonic TNF-α and LTB_4 production, antioxidant activity	[52]
Short-chain fatty acids	Acetate, propionate, butyrate	Inhibited LPS-stimulated release of TNF-α, inhibited NF-κB activity, reduced MPO activity, IL-6 protein release	[53]

Solid lipid nanoparticles	Cholesteryl butyrate, dexamethasone-loaded solid lipid nanoparticles	Cholesterylbutrate = decreased IL-1β and TNF-α secretion, increased IL-10 secretion; dexamethasone-loaded solid lipid nanoparticles = decreased IL-1β, TNF-α, and IL-10 secretion	[54]
ω-3 fatty acid	EPA	Reduced TNF-α, IL-6 expression, increased IL-10 expression	[55]
PUFA	EPA, γ-linolenic acid, stearidonic acid	Decreased PGE_1 and LTB_4	[56]
PUFA	α-Linolenic acid deficiency	Induce the increase of IL-6, TNF-α, and central serotonin (5-HT)	[57]
ω-3 fatty acid	α-Linolenic acid	Decreased the expression of ICAM-1, VCAM-1, and VEGFR-2	[58]
ω-3 fatty acid	DHA and EPA	Increased expression of the anti-inflammatory PGE_2 receptor EP3	[59]
Krill oil	omega-3 PUFA	Increased PGE_3, PPAR-γ coactivator 1 α	[60]
Probiotic organisms			
Administered *L rhamnosus* strains	*L rhamnosus*	Stimulation of the immune system by lactobacilli	[61]
Administered *Lactobacillus* spp.	*Lactobacillus paracasei*, *Lactobacillus reuteri*	Decreased TNF-α, reduced mucosal IL-12 mRNA	[62]
Administered probiotics	*Lactobacillus casei*, *Lactobacillus acidophilus* and *Bifidobacterium lactis*	Lower incidence of diarrhea in *B lactis*, *B lactis* reduced TNF-α production, iNOS, COX-2 expression, *L acidophilus*, reduced LTB_4 production, iNOS expression	[63]
Administration of *Lactobacillus plantarum* 299v (*L plantarum*)	*L plantarum*	Decreased mucosal IL-12, IFN-γ	[64]
Administration of VSL#3	VSL#3 (VSL Pharmaceuticals, Gaithersburg, MD, USA)	Reduction in mucosal secretion of TNF-α, IFN-γ, protected the epithelium against pathogenic bacterial invasion	[65]
Administration of VSL#3	VSL#3	Toll-like receptor-9 mediated anti-inflammatory effect of DNA	[66]
Bifidobacterium breve strain Yakult and *Bifidobacterium bifidum* strain Yakult	*B breve*, *B bifidum*	Induced secretion of IL-10, inhibited TNF-α–induced secretion of IL-8	[67]
Dietary Lactibiane Tolerance	*Lactobacillus salivarius*	Reducing the IL-12, increasing the IL-10.	[68]
Dietary *L acidophilus* with olsalazine	*L acidophilus*	Reduced serum levels of C-reactive protein, TNF-α, IL-6	[69]
Dietary probiotic yogurt	*L rhamnosus* and *L reuteri*	Decreased serum IL-12, percentage of TNF-α, IL-12 producing	[70]
Dietary probiotics powder	*Bifidobacterium fifidum*	Inhibited IFN-γ, MCP-1, slightly increased IL-10 production, reduced levels of TNF-α	[37]
Fed *L casei* strain Shirota	*L casei*	Increased colonic epithelial regeneration	[71]
Fed *Saccharomyces boulardii*	*S boulardii*	Decreased activation level of NF-κB, diminution of $CD4^+$ T-cell infiltration, inhibited production of IFN-γ	[72]
L casei strain shirota	*Lactobacillus*	Down-regulated the IL-6 and IFN-γ	[73]
Probiotic organisms in milk	*L salivarius*	Reduced fecal coliform and enterococci, reduced *Clostridium perfringens*, modulation of the gastrointestinal flora	[74]
*Bifidobacterium*strains	*B bifidum* Bif1, Bif2, Bif3; *Bifidobacterium longum* Lon4, Lon5, Lon6; *Bifidobacterium catenulatum* Cat7, Cat8, Cat9; *B breve* Bre10, Bre11; and *Bifidobacterium adolescentis* Ado12	Inhibited TNF-α, IL-8 production	[75]
Lactic acid bacterium	*Pediococcus acidilactici*	Induced IL-10 producing	[76]
Dietary *Lactobacillus*	*L plantarum*	Increased the total *Bifidobacteria* and *Lactobacilli*, decreased *Enterococci* and *C perfringens*	[77]
Dietary probiotic bacteria	*Bifidobacteria* and *Lactobacillus*	Increase in the levels of IgE and IgM	[78]
Probiotic	*L plantarum* Lp91	Down-regulated TNF-α and COX-2, up-regulated IL-10	[79]
Dietary fibers			
Dietary fiber	Propionate, butyrate	Decreased NO, LTB_4, and TNF-α; inhibition of NF-κB activation	[80]
Dietary fiber	Soluble corn fiber, STA-LITE III polydextrose, biogum, pullulan, RROMITOR	RROMITOR resistant starch-75 and inulin decreased IFN-γ production; soluble corn fiber, STA-LITE III polydextrose; biogum, pullulan and RROMITOR resistant	[81]

(*continued on next page*)

Table 2 *(continued)*

Products	Active compounds	Active factors	Reference
	(Tate and Lyle Ingredients America, Decatur, IL, USA) resistant starch-75, inulin	starch-75 up-regulated colonic PPAR-γ expression	
Dietary fiber	Orange pulp, guar gum, mixture of grange pulp and guar gum	Mixture of orange pulp and guar gum increased PGE_2 level, steoprotegerin decreased serum gastrin levels	[82]
Dietary fiber	Germinated barley foodstuff	Enhanced luminal butyrate production and thereby accelerate colonic epithelial repair in colitis	[83]
Dietary fiber	Fibers	Butyrate-induced suppression of NF-κB activation	[84]
Dietary pectin	Pectin	Increased IFN-γ and IL-2 concentration	[85]
Dietary pectin	Pectin	Reduced TNF-α, GATA-3, IgG, and IgM	[86]
Dietary fiber	Fermentable dextrin fiber	Inhibited IL-1β, down-modulated plasmatic IL-12 and TNF-α	[87]
Dietary fiber	Germinated barley foodstuff	Decreased TNF-α, IL-6, and IL-8	[88]
Dietary fiber	Enzyme-treated rice fiber	Decrease colonic mucosal damage and 5-HT production, attenuated the T-cell activation ($CD4^+$ $CD69^+$)	[89]
Dietary fiber	Germinated barley foodstuff	Decreased the cecal succinate content, increased β-glucosidase activity	[90]
Dietary chitin	Chitin	Suppressed MPO activation in the colon and decreased serum IL-6 concentrations	[91]
Drugs			
5-ASA	5-ASA	Increased PPAR-γ expression, decreased NF-κB activity	[92]
5-ASA	5-ASA	Inhibition of NF-κB activity, inhibition of intestinal epithelial cell injury, inhibition of apoptosis induced by oxidative stress, reduced synthesis of prostaglandins and leukotrienes	[93]
5-ASA	5-ASA	Reduced MPO activity and TNF-α levels, increased colonic hemeoxygenase enzyme activity, induced colonic HO-1 protein expression, stimulated hemeoxygenase enzyme activity	[94]
5-ASA	5-ASA	Decreased MPO activity	[95]
5-ASA	5-ASA	Decreased MPO activity	[96]
5-ASA	5-ASA	Inhibited β-catenin activation	[97]
5-ASA–loaded *N*-succinyl-chitosan microparticles and freeze-dried systems	5-ASA	Decreased MPO activity	[98]
5-ASA with antioxidant	5-ASA, ascorbic acid, phenyl butylnitrone, α-tocopherol	Decreased MPO activity	[99]
Corticosteroids	Corticosteroids	Block the generation of proinflammatory cytokines and chemokines including IL-1β, IL-4, IL-5, IL-8, granulocyte-macrophage colony stimulating factor, and TNF-α	[100]
Taurine-conjugated 5-aminosalicylic acid and colon-specific prodrug	5-ASA	Inhibited IL-1β–mediated NF-κB–dependent luciferase expression and IL-6 secretion, inhibited IL-1β–mediated NF-κB activation	[101]
5-ASA	5-ASA	Decreased MPO activity	[102]
Microspheres prepared with chitosan and 5-ASA	5-ASA	Decreases the content, synthesis, and release of IL-1 and IL-1β; reduced ILs mRNA levels	[103]
5-ASA with hyperbaric oxygen	5-ASA	Decreased MPO activity	[104]
Amide conjugate 4-aminosalicylic acid	4-Aminosalicylic acid	Decreased MPO activity	[105]
5-ASA	5-ASA	Down-regulated TNF-α and IL-1β–induced COX-2, decreased PGE_2 synthesis	[106]

ALT, alanine aminotransferase; AP-1, activator protein-1; AST, aspartate aminotransferase; GATA-3, guanine adenine thymine adenine-3; ICAM-1, intercellular adhesion molecule-1; IFNG, interferon gamma; LTB_4, leukotrienes B_4; MCP-1, monocyte chemotactic protein-1; TLR4, toll-like receptor 4; VCAM-1, vascular cell adhesion molecule-1; VEGFR, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

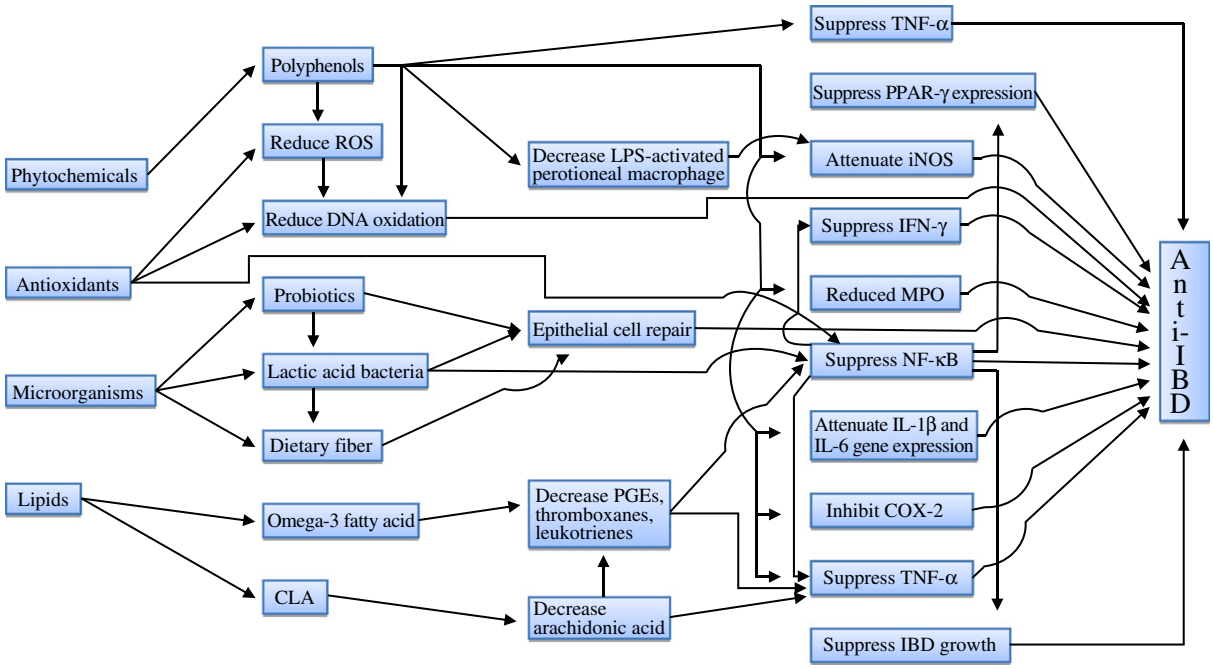

Fig. 1 – Summary of the natural compounds, active components, and potential mechanisms of actions on IBD. Refer to Tables 1 and 2 and the text for more details.

especially cytokine modulation, of natural products on IBD. The "Cytokines and IBD" section is provided because one of the main causes of IBD is thought to be an imbalance in proinflammatory cytokines. Table 1 is a summary of the active compounds present in natural products and their target IBD-related cytokines. Table 2 is a description of all natural products that are reported to have anti-IBD activity and their active factor. Fig. 1 is a summary of the various anti-IBD mechanisms of these natural products.

This review reveals that many natural products possess anti-IBD activity because they are able to modulate the function of cytokines. Plant-based materials such as phytochemicals were the most abundant anti-IBD materials studied, although certain lipids and dietary fibers also had anti-IBD effects. In addition, microorganisms, particularly lactic acid bacteria, can have some anti-IBD activity. The main active compounds in anti-IBD phytochemicals were phenolic compounds and flavonoids, and the anti-IBD effects of lipids are attributable to the n-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

The IBD condition is largely influenced by cytokines. In this review, we found that the anti-IBD effect of phytochemicals was primarily attributed to their inhibition of TNF-α, IL-1, IL-6, iNOS, and myeloperoxide (MPO), peroxisome proliferator–activated receptor-γ (PPAR-γ), TNF-α, IL-6, and prostaglandin E (PGE). The dietary fibers reduced the levels of TNF-α, NO, and IL-2. The lactic acid bacteria reduced IFN-γ, IL-6, IL-12, TNF-α, and NF-κB levels, whereas 5-ASA, an anti-IBD drug, reduced MPO and NF-κB activity. These results indicate that natural products can be used as effective anti-IBD treatments. However, more research is needed to examine the effects of these natural products on IBD and to establish their mechanisms of action before new anti-IBD drugs can be developed. As shown in Table 1, many natural materials have anti-IBD effects, and the anti-IBD effects of natural products seem to largely target TNF-α, IL-6, or iNOS. The cytokines IL-8, IL-2, and IL-4 have less influence on IBD and are likely a target of lower importance.

3. Cytokines and IBD

Cytokines play an important role in IBD because they are key signaling molecules of the intestinal immune system [1]. Cytokines are small proteins produced mainly by immune cells that facilitate communication between cells, stimulate the proliferation of antigen-specific effector cells, and mediate local and systemic inflammation using the autocrine, paracrine, and endocrine pathways [1,107]. Tumor necrosis factor α is one of the most important proinflammatory cytokines and can directly influence intestinal epithelial tissue [4]. Tumor necrosis factor α secretion results in the disruption of the epithelial barrier, induction of apoptosis in epithelial cells, and induction of chemokine secretion by intestinal epithelial cells [4]. Liu and Wang [26] reported that TNF-α that is released from macrophages during the early inflammatory response plays an important role in 2,4,6-trinitrobenzenesulfonic acid (TNBS)–induced colitis and is likely the key regulator of the inflammatory cascade in this model of IBD.

Interleukin-1ß and IL-6 are key mediators of IBD progression [4]. An IL-1 receptor antagonist was shown to suppress the infiltration of inflammatory cells into the large intestine, the MPO activity of cells in areas of edema, and large intestinal necrosis in animals with acute experimental colitis [108]. In addition, an antimurine IL-1ß antibody attenuated not only

the pathological symptoms of dextran sulfate sodium (DSS)–induced colitis but also IL-6 messenger RNA (mRNA) expression [38]. Interleukin-6 stimulates neutrophil chemotaxis and is associated with necrosis in the colon, which, in turn, leads to tissue destruction [26]. Interleukin-10 is another essential cytokine with well-established immunoregulatory activity, which has been confirmed in vitro and in vivo using several animal models. In humans, an intravenous injection of IL-10 in healthy human volunteers was well tolerated and had inhibitory effects on T cells and suppressed production of the proinflammatory cytokines TNF-α and IL-1β [68].

Nuclear factor κB is part of an important signaling pathway with a pivotal role in regulating a vast number of genes involved in both the inflammatory response and cell survival, including proinflammatory cytokine elaboration, cell death, and survival proteins; intercellular adhesion molecules; COX-2; and iNOS [109]. Zhang et al [110] reported that NF-κB activation plays a central role in the regulation of gene transcription of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, COX-2, iNOS, and adhesion molecules during the UC inflammatory process. An earlier study [111] showed that NF-κB inhibitors decrease inflammation in an IBD animal model, confirming its pivotal role. Thus, inhibiting NF-κB activity might help alleviate the severity of IBD [112,113]. An optimal therapeutic strategy that could attenuate the NF-κB pathway (an upstream target) during the inflammation cascade by blocking simultaneous expression of multiple proinflammatory genes might be more effective than suppressing individual factors such as TNF-α, IL-1β, or IL-6 to treat UC [26,114]. Up-regulation of PPAR-γ has also been recognized as a potential target for controlling intestinal inflammation [115]. For example, enhanced PPAR-γ activity has potent anti-inflammatory effects, which may be caused by its ability to interfere with NF-κB activation [115] and may be a potential pathway for control of IBD.

Proinflammatory and anti-inflammatory cytokines and the expression of inflammatory proteins including COX-2 and iNOS, which are expressed during the early responses to proinflammatory mediators and mitogen stimuli, play an important role in IBD pathophysiology [116]. Recent studies suggest that the activation of mitogen-activated protein kinases such as c-Jun N-terminal kinase (JNK) plays an important role in intestinal inflammation in patients with IBD [117]. c-Jun N-terminal kinase regulates the maturation and activity of T cells and the synthesis of proinflammatory cytokines including IL-2, IL-6, and TNF-α [117]. Thus, the JNK pathway is a potentially relevant target for inflammatory disease therapy.

4. Phytochemicals and IBD

Several investigators have reported anti-inflammatory properties of many different types of phytochemical compounds. For example, the large groups of flavonoid compounds, which are plant secondary metabolites and ubiquitously distributed throughout the plant kingdom, are known to possess antioxidative and anti-inflammatory activities in cell cultures and rodent models [38]. Flavonoids generally exhibit potent antioxidative/radical scavenging effects [118]. Rutin, found in various foods such as buckwheat, parsley, tomatoes, and apricots, is one of the most common naturally occurring flavonoids with a wide range of biological activities [119]. Oral administration of rutin suppresses the colonic damage and inflammation associated with acetic acid–induced colitis in rats [120]. Kwon et al [38] reported that dietary rutin is very effective at attenuating DSS-induced colitis in mice, which likely occurs by attenuating proinflammatory gene expression, particularly that of IL-1β and IL-6. These researchers also reported that oral administration of rutin, 3 days after initiating DSS treatment, significantly reversed colitis, as measured by colorectal shortening and IL-1β production. Thus, rutin is effective as both a prophylactic and a therapeutic agent for treating UC [38]. Moreover, dietary rutin, even at low doses, attenuates the production of critical proinflammatory mediator genes such as IL-1β and IL-6, granulocyte-macrophage–stimulating factor, and iNOS, thereby ameliorating DSS-induced colitis in mice [38].

Green tea polyphenols are antioxidants that prevent the activation and transcription of NF-κB and inducible kinases in fetal rat intestinal epithelial cells and in an IL-2–deficient mouse model of autoimmunity and IBD [13]. Catechins are polyphenolic flavonoid plant metabolites with antioxidant properties that have been evaluated in preclinical IBD models with promising results [121]. These findings are supported by in vitro and in vivo studies in which catechins reduced the levels of several inflammatory mediators [122]. The polyphenol epigallocatechin-3-gallate (EGCG) blocks the activation of the transcription factor, NF-κB, in intestinal epithelial cells [123]. Ran et al [124] reported that EGCG ameliorates mucosal inflammation by inhibiting TNF-α, IFN-γ, and NF-κB p65 production and that EGCG, a catechin from green tea, reduces the severity of colitis and significantly reduces MPO activity in comparison with vehicle treatment [29].

Inducible enzymes such as COX-2 and iNOS are predominantly expressed at sites of inflammation [9]. Increased amounts of these proteins have been found in animal models of experimental colitis [116]. In vitro studies have shown that polyphenols including catechins inhibit COX-2 expression. In addition, aflavin monogallate from black tea has been demonstrated to suppress COX-2 in human colon cancer cells [125]. Catechins have COX-1and COX-2 inhibitory activity in various human and mouse cell lines [9]. Peng et al [126] reported decreased COX-2 expression levels in colon cancer cells after treatment with low concentrations of EGCG. Moreover, EGCG decreases iNOS activity and protein levels in lipopolysaccharide (LPS)-activated peritoneal macrophages [127].

Curcumin has strong anti-inflammatory effects and can inhibit the onset and progression of neurodegenerative diseases such as Alzheimer and various cancers [128]. Curcumin is a strong inducer of the heat shock response, a strong antioxidant, and inhibits COX-2, lipooxygenase, NF-κB, and the T-helper 1 (Th1) profile of $CD4^+$ T cells [128]. Silva et al [9] reported that *Abarema cochliacarpos* treatment ameliorates colonic lesions and histologic signs of damage, reduces neutrophil infiltration, decreases TNF-α, and down-regulates COX-2 and iNOS proteins and JNK activation in colonic tissue. They also noted that MPO activity and TNF-α levels are correlated with the development of colonic inflammation. However, *A cochliacarpos* treatment reduced both parameters

and consequently ameliorated colonic damage [9]. Cho et al [4] suggested that the potent anti-inflammatory effects of *Patrinia scabiosaefolia* extract in mice with DSS-induced colitis are mediated by the inhibition of proinflammatory mediator production. Furthermore, *P scabiosaefolia* extract (50 mg/kg) had better therapeutic efficacy than did 5-ASA (75 mg/kg), which is currently used to treat IBD. Lee et al [44] reported that capsaicin modulates the NF-κB and IL-8 pathways, thereby inhibiting IL-8 production. Moreover, capsaicin further inhibits TNF-α production, which might be mediated by PPAR-γ activation [129]. As mentioned earlier, many phytochemicals have been shown to have anti-IBD effects in several models over the last decade. The main mechanisms for the anti-IBD effect of phytochemicals fall into 2 main categories: antioxidative effects (through free radical scavenging) and inhibition of TNF-α, NF-κB, IFN-γ, COX-1/COX-2, or iNOS. However, the mechanism by which phytochemicals modulate cytokine production are unknown and remain controversial; thus, as one would expect, only a few of these materials have been used to treat IBD in clinical settings.

5. Antioxidants and IBD

The various forms of IBD are characterized by high levels of reactive oxygen species (ROS) produced by neutrophils and macrophages that are recruited to the inflamed epithelial tissues, combined with a decreased antioxidant capacity in the plasma [35]. Oxidative stress is thought to be a major cause of tissue destruction in patients with IBD [130], and reactive oxygen and nitrogen metabolites are involved in the initiation and progression of IBD [131]. Reactive oxygen species are extremely unstable because of their high reactivity, which may result in lipid peroxidation and the oxidative damage to DNA and proteins [132]. This activity has implicated ROS in the tissue destruction observed in IBD [13]. Shiratora et al [133] reported that the colons of patients with IBD produce more oxygen free radicals than those of healthy subjects. Several studies have suggested that IBD develop because of an imbalance between prooxidant and antioxidant compounds. Liu and Wang [26] suggested that iridoid glycosides likely have protective effects during UC through scavenging free radicals and for their antioxidant properties. This may be an important underlying mechanism through which iridoid glycosides protect against UC. Myeloperoxide, an enzyme present in neutrophils, catalyzes the formation of potent cytotoxic oxidants such as hypochlorous acid, from hydrogen peroxide (H_2O_2), chloride ions, and N-chloramines [26]. Furthermore, MPO activity reflects the degree of neutrophil infiltration during the intestinal inflammatory process [134]. Liu and Wang [26] reported that iridoid glycosides inhibit increases in MPO activity in a TNBS-induced colitis model in a dose-dependent manner. The tripeptide glutathione is the most important intracellular defense against oxidative stress and is essential for both the functional and structural integrity of the gut [13]. Glutathione may be depleted during inflammatory illnesses, and tripeptide glutathione–deficient mice show severe degradation in the jejunum and colonic mucosa, loss of body weight, and development of diarrhea [135]. The natural flora release numerous antioxidants from consumed plants, including important antioxidants such as glutathione and folic acid [128]. Khan et al [136] reported that the anti-inflammatory effects of green tea are attributable to the polyphenol fraction, which is rich in antioxidants.

5-Aminosalicylic acid and mesalazine are widely used to treat several forms of IBD, particularly UC and CD [137]. 5-Aminosalicylic acid is a potent free radical scavenger [138] that has antioxidant properties and can inhibit PGE synthesis and reduce NF-κB activation [99]. Ancha et al [99] reported that a combination of antioxidants and 5-ASA in an enema formulation, significantly augmented the anti-inflammatory activity of mesalamine in treating TNBS-colitis. They also suggested that antioxidant and anti-inflammatory drug combination therapies might have potential for treating IBD.

Oxidative stress arises when there is a marked imbalance between the production of ROS and their removal by antioxidants [139]. In reaction to mild oxidative stress, tissues often respond by producing more antioxidants. However, severe and persistent oxidative stress depletes the antioxidant reserves of tissues and overtakes their ability to produce more antioxidants, leading to lower antioxidant levels and tissue injury [139]. Patients with IBD demonstrate decreased expression of the antioxidant heme oxygenase-1 (HO-1) in the intestinal epithelium of inflamed colonic mucosa relative to controls, suggesting that HO-1 expression is dysregulated during inflammation [140]. Heme oxygenase-1 is the rate-limiting enzyme of heme catabolism, which generates biliverdin, iron, and carbon monoxide and has been shown to have important anti-inflammatory properties [139].

Immune cell activation and the release of ROS such as H_2O_2 are prominent early events in the pathogenesis of IBD that could affect the enteric nervous system. There is a close parallel between the loss of enteric neurons and their axons after exposure to H_2O_2 in vitro and the damage to the enteric nervous system that is observed in the acute phase of initiation of colitis in vivo, in which a significant loss of neurons occurs within 24 hours [141]. Enhanced ROS production and oxidative injury play a critical role in the onset and progression of neurodegenerative disorders [139]. To maintain a proper redox balance, the central nervous system is equipped with endogenous antioxidant enzymes as an antioxidant defense mechanism [139]. Of note, we found many antioxidant materials from natural products such as ascorbic acid, carotenoids, catechin, ellagic acid, gallic acid, gingerols, kaempferol, quercetin, rutin, and tannins. It is possible that the anti-IBD effects of these natural products could be related to antioxidative effects similar to 5-ASA. Thus, antioxidants may be useful in developing novel drugs for IBD therapy.

6. Microorganisms and IBD

Probiotics actively interfere with the anti-inflammatory and proinflammatory signaling pathways, inducing production of IL-10 and reducing INF-γ and TNF release [68]. Treating mice in the acute DSS-induced colitis model with antibiotics, prebiotics, and probiotics reduces disease symptoms and prevents inflammation [142]. Larrosa et al [35] reported that pomegranate extract and the microbiota-derived metabolite

urolithin-A administered for 20 days before colitis induction resulted in an increase in lactobacilli and bifidobacteria. They suggested that this could be an indirect effect of a phenolic-supplemented diet that increases bifidobacterium, lactobacillus, and clostridium counts and prevents the colonization and invasion of tissues by enterobacteria, including *Escherichia coli*. Stimulating the lactobacillus and bacteroides growth through amino acid supplementation promotes epithelial repair in the murine DSS-induced colitis model [131,143,144]. A previous study indicated that bifidobacterium and lactobacillus are also effective in modulating the proinflammatory response of intestinal epithelial cells after challenge by pathogenic enterobacteria [35,145]. The intestinal bacterial flora are deeply involved in the pathogenesis of human IBD, although the exact presence of unwanted bacteria or lack of specific beneficial bacteria has not been described [128]. It is interesting that the incidence of CD, not UC, increases with reduced seroprevalence of *Helicobacter pylori* [143]. Millions of different nutrients, vitamins, and antioxidants are released and absorbed as a result of microbial enzymes in the intestine [128].

The main anti-IBD effect of microorganisms may be due to their ability to regulate certain cytokines (IL-10, INF-γΓ, and TNF-α) and to protect against oxidative damage or promote epithelial repair. Alternately, probiotics might function by modulating cell proliferation and apoptosis [144]. *Lactobacillus rhamnosus* GG and *Clostridium butyricum* administration to rats was shown to increase epithelial cell proliferation rates in the small intestine, cecum, and distal colon [146]. This increase in epithelial cell proliferation is possibly caused by the ability of these probiotic strains to produce short-chain fatty acids for cells via the fermentation of polysaccharides [146].

As mentioned previously, NF-κB is required for the transcriptional activation of a number of inflammatory mediators including IL-8, TNF-α, IL-6, COX2, and iNOS, among others, and its dysregulation has been observed in many inflammatory diseases [147]. A number of lactic acid bacteria have been shown to suppress inflammatory signals mediated by NF-κB [147]. By increasing IL-10 levels and, consequently, decreasing inflammatory cytokines such as TNF-α and IFN-γ, some lactic acid bacteria can prevent the appearance of local inflammatory diseases and could be used as an adjunct therapy with conventional treatments [147]. These results are in agreement with the observation that administering probiotic yogurt containing live *Lactobacillus delbrueckii* and *Streptococcus thermophilus* can modulate the immune response, inducing down-regulation of the inflammatory cytokines (IL-17 and IL-12) produced by immune cells involved in the inflammatory process [147]. Some investigations have pointed to a role for anaerobic bacteria such as bacteroides or clostridium [148]. For instance, IL-10–deficient mice develop colitis under conventional housing conditions but not under germ-free conditions [149]. At 2 weeks of age, before the development of colitis, increased numbers of clostridium bacteria were found adhering to the colonic mucosa of these mice [149].

Disruption of the gut epithelial barrier increases permeability, leading to inappropriate activation of the mucosal immune system in patients with IBD [149]. Proinflammatory bacterial components can penetrate the gut epithelium after the breakdown of the intestinal barrier and can induce chronic inflammation [150]. The proinflammatory cytokines, TNF-α and IFN-γ, can increase paracellular leakage and inhibit the expression of cytoprotective heat shock proteins 25 and 70, rendering the intestinal epithelial cells susceptible to future shock and increasing the likelihood of apoptosis. Two proteins secreted by *L rhamnosus*, p40 and p75, have been shown to inhibit this proapoptotic TNF-α–mediated process [150]. Probiotic bacteria are also believed to modulate the mucosal barrier by increasing the release of defensins, mucins, and proteins associated with tight junctions such as the claudins and occludins [150] A parallel increase in antibiotic use and CD incidence has been associated with decreased numbers of beneficial bacteria (such as bifidobacterium, lactobacillus, bacteroidetes, and firmicutes), which allows for increased numbers of pathogenic bacteria (such as invasive *E coli*) to adhere to and invade the intestinal epithelium [151]. Interestingly, previous studies reported that probiotics such as *Lactobacilli* and *Bifidobacteria* have anti-inflammatory effects, which were associated with modulating the immune response, down-regulating inflammatory cytokines, and establishing equilibrium with beneficial bacterial. Probiotic inhibition of TNF-α, INF-γ, or NF-κB and modulation of cell proliferation and apoptosis appear to be especially important mechanisms behind their anti-IBD effects.

7. PUFAs and IBD

Many studies have reported that fatty acids, particularly omega-3 PUFAs, have anti-inflammatory effects. In general, fish oil is a rich source of omega-3 PUFAs such as EPA and DHA [8]. These fatty acids inhibit the formation of proinflammatory cytokines [152], and several studies have reported that omega-3 PUFAs help reduce inflammation in patients with CD and UC. Esteve-Comas et al [153] reported that patients with active and inactive CD and UC had significantly increased plasma levels of omega-3 and omega-6 PUFAs, but the pathogenic significance of this finding is not fully understood [128]. Serhan et al [154] reported that omega-3 PUFAs (DHA and EPA) elicit potent anti-inflammatory and immunoregulatory effects, both directly and following transcellular processing, which results in the generation of hydroxyl-containing omega-3 PUFA metabolites. Omega-3 PUFAs metabolites such as eicosanoids are key mediators and regulators of inflammation [155], including PGEs, thromboxanes, leukotrienes, and other oxidized derivatives [156].

Calder [156] reported that increased consumption of long-chain omega-3 PUFAs such as EPA and DHA can result in increased proportions of these fatty acids in inflammatory cell phospholipid bilayers. The incorporation of EPA and DHA into human inflammatory cells occurs in a dose-response manner that occurs partly at the expense of arachidonic acid [156]. The subsequent decrease in arachidonic acid results in a decreased production of PGE, thromboxane, 5-hydroxyeicosatetraenoic acid, and leukotrienes by inflammatory cells [156]. The reduced generation of arachidonic acid–derived mediators that accompanies fish oil consumption has led to the hypothesis that fish oil is anti-inflammatory and may be useful in preventing or treating inflammatory conditions

[156]. As mentioned previously, arachidonic acid may promote intestinal inflammation by regulating the inflammatory response, leading to high levels of cytokines, eicosanoids, free radicals, PGE, thromboxanes, and leukotrienes [157]. Therefore, the reduction of arachidonic acid that occurs after dietary omega-3 PUFA consumption may be the main mechanism behind the anti-IBD effects of omega-3s.

Bassaganya-Riera et al [41] reported that conjugated linoleic acid (CLA) also has anti-inflammatory effects. Dietary CLA modulates PPAR-γ and δ-responsive gene expression and suppresses NF-κB activation in the colons of mice undergoing DSS-induced colitis [41]. Peroxisome proliferator–activated receptor-γ activation by CLA decreases colonic TNF-α expression by blocking NF-κB activation, and CLA ameliorates LPS-induced TNF-α production and cachexia in mice [41]. Bassaganya-Riera et al [41] found that the beneficial effects of CLA in dextran sodium sulfate–induced colitis were abrogated in tissue-specific PPAR-γ–deficient mice that only lack PPAR-γ in hematopoietic and epithelial cells. Conjugated linoleic acid also delays the onset of experimental IBD and attenuates growth suppression in pigs by activating colonic PPAR-γ, whereas omega-3 PUFAs accelerate remission by activating PPAR-δ. Furthermore, the combination of CLA and omega-3s was able to accelerate recovery by activating PPAR-δ and up-regulating the expression of keratinocyte growth factor [41].

Tedelind et al [53] reported that short-chain fatty acids such as acetate and propionate also have anti-IBD effects. Short-chain fatty acids inhibit LPS-induced TNF-α release but not IL-8 secretion. Furthermore, butyrate inhibits TNF-α–mediated activation of the NF-κB pathway in a human colon adenocarcinoma cell line [53]. Shoda et al [158] reported that an increased dietary intake of omega-6 PUFAs such as CLA correlates with an increased incidence of CD, whereas an oleic acid–enriched olive oil diet may reduce the inflammatory response, which is associated with increased IL-8 levels [153,159]. Therefore, replacing CLA with oleic acid in the diet of patients with CD, in combination with a diet rich in antioxidants, could be beneficial for decreasing inflammatory activity [153,159]. The anti-IBD effect of lipids such as omega-3 PUFAs and CLA include both cytokine regulation and decreased PGE production. Peroxisome proliferator–activated receptor-γ agonists are potential therapeutic agents for treating IBD, and many lipids and eicosanoids are plausible endogenous ligands for PPAR-γ. Electrophilic lipids that can bind to a critical thiol residue (Cys285) within the ligand-binding domain, can form a covalent bond, and can prolong receptor activation appear to be the best candidates [160].

A key mechanism by which EPA exerts its anti-inflammatory activity appears to be NF-κB suppression[161]. This may occur by reducing phosphorylation of NF-κB, thereby leading to reduced degradation of the inhibitory IκBα complex [162]. Others have suggested that the highly polyunsaturated EPA could be readily oxidized, and oxidized EPA could then interfere with NF-κB activation [162]. Eicosapentaenoic acid has been found to attenuate IL-6 production in a PPAR-γ–dependent manner in glioma cells [163]. Draper et al [164] reported that the EPA-mediated effects on IL-12 cytokine production were independent of PPAR-γ but involved both increased PPAR-$\gamma\Gamma$ expression and NF-κB suppression [162]. The main mechanism behind the anti-IBD effect of PUFAs may be TNF-α inhibition by blocking NF-κB.

8. Conclusions

In this review, we found that the main mechanism of the anti-IBD effect of natural products was through modulating cytokine activity. Cytokines can up-regulate and/or down-regulate several genes and their associated transcription factors, which may lead to a reduction in IBD symptoms. The anti-IBD effects of these natural products are largely mediated by TNF-α, NF-κB, IL-6, or iNOS, whereas IL-8, IL-2, and IL-4 have less of an influence on IBD. The main active components of anti-IBD phytochemicals are phenolic compounds and flavonoids, and the anti-IBD effect of lipids is closely correlated with the omega (n-3)PUFA content, particularly DHA and EPA. Moreover, the anti-IBD effects of dietary fiber are related to an increase in short-chain fatty acids. These results indicate that natural products such as phytochemicals, antioxidants, probiotics, dietary fiber, and lipids may be useful for treating IBD. However, only a few of these substances have been used as anti-IBD drugs over the last decade. The exact mechanisms behind the anti-IBD effects of these natural products are still unclear, and additional research will be needed to examine their effects and to determine which specific factors are related to ameliorating IBD in humans.

Acknowledgment

This paper was supported by Konkuk University in 2011.

REFERENCES

[1] Sanchez-Muñoz F, Dominguez-Lopez A, Yamamoto-Furusho JK. Role of cytokines in inflammatory bowel disease. World J Gastroenterol 2008;14:4280–8.
[2] Ueda Y, Kawakami Y, Kunii D, Okada H, et al. Elevated concentrations of linoleic acid in erythrocyte membrane phospholipids in patients with inflammatory bowel disease. Nutr Res 2008;28:239–44.
[3] Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. Drugs 2005;65:2253–86.
[4] Cho E-J, Shin J-S, Noh Y-S, Cho Y-W, et al. Anti-inflammatory effects of methanol extract of *Patrinia scabiosaefolia* in mice with ulcerative colitis. J Ethnopharmacol 2011;136:428–35.
[5] Sergent T, Piront N, Meurice J, Toussaint O, Schneider Y-J. Anti-inflammatory effects of dietary phenolic compounds in an in vitro model of inflamed human intestinal epithelium. Chem Biol Interact 2010;188:659–67.
[6] García-Lafuente A, Guillamón E, Villares A, Rostagno M, Martínez J. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflamm Res 2009;58:537–52.
[7] Rahman I, Biswas SK, Kirkham PA. Regulation of inflammation and redox signaling by dietary polyphenols. Biochem Pharmacol 2006;72:1439–52.

[8] Koretz RL, Rotblatt M. Complementary and alternative medicine in gastroenterology: the good, the bad, and the ugly. Clin Gastroenterol Hepatol 2004;2:957–67.
[9] da Silva MS, Sánchez-Fidalgo S, Talero E, Cárdeno A, et al. Anti-inflammatory intestinal activity of *Abarema cochliacarpos* (Gomes) Barneby & Grimes in TNBS colitis model. J Ethnopharmacol 2010;128:467–75.
[10] Chen H-J, Chung C-P, Chiang W, Lin Y-L. Anti-inflammatory effects and chemical study of a flavonoid-enriched fraction from adlay bran. Food Chem 2011;126:1741–8.
[11] Mandalari G, Bisignano C, Genovese T, Mazzon E, et al. Natural almond skin reduced oxidative stress and inflammation in an experimental model of inflammatory bowel disease. Int Immunopharmacol 2011;11:915–24.
[12] Park M-Y, Kwon H-J, Sung M-K. Dietary aloin, aloesin, or aloe-gel exerts anti-inflammatory activity in a rat colitis model. Life Sci 2011;88:486–92.
[13] Oz HS, Chen TS, McClain CJ, de Villiers WJS. Antioxidants as novel therapy in a murine model of colitis. J Nutr Biochem 2005;16:297–304.
[14] Yoshioka Y, Akiyama H, Nakano M, Shoji T, et al. Orally administered apple procyanidins protect against experimental inflammatory bowel disease in mice. Int Immunopharmacol 2008;8:1802–7.
[15] D'Argenio G, Mazzone G, Tuccillo C, Ribecco MT, et al. Apple polyphenols extract (APE) improves colon damage in a rat model of colitis. Dig Liver Dis 2012;44:555–62.
[16] Ko JK-S, Chik CW-S. The protective action of radix *Astragalus membranaceus* against hapten-induced colitis through modulation of cytokines. Cytokine 2009;47:85–90.
[17] Maity S, Ukil A, Karmakar S, Datta N, et al. Thearubigin, the major polyphenol of black tea, ameliorates mucosal injury in trinitrobenzene sulfonic acid–induced colitis. Eur J Pharmacol 2003;470:103–12.
[18] Jagtap AG, Niphadkar PV, Phadke AS. Protective effect of aqueous extract of *Bombax malabaricum* DC on experimental models of inflammatory bowel disease in rats and mice. Indian J Exp Biol 2011;49:343–51.
[19] Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A. Pure compound from *Boswellia serrata* extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFα, IL-1β, NO and MAP kinases. Int Immunopharmacol 2007;7: 473–82.
[20] Cheon MS, Yoon T, Lee DY, Choi G, et al. *Chrysanthemum indicum* Linné extract inhibits the inflammatory response by suppressing NF-κB and MAPKs activation in lipopolysaccharide-induced RAW 2647 macrophages. J Ethnopharmacol 2009;122:473–7.
[21] Kang C-H, Choi YH, Park S-Y, Kim G-Y. Anti-inflammatory effects of methanol extract of *Codium fragile* in lipopolysaccharide-stimulated RAW 264.7 cells. J Med Food 2012;15:44–50.
[22] Paiva LAF, Gurgel LA, Silva RM, Tomé AR, et al. Anti-inflammatory effect of kaurenoic acid, a diterpene from *Copaifera langsdorffii* on acetic acid–induced colitis in rats. Vascul Pharmacol 2002;39:303–7.
[23] Han ES, Oh JY, Park H-J. *Cordyceps militaris* extract suppresses dextran sodium sulfate–induced acute colitis in mice and production of inflammatory mediators from macrophages and mast cells. J Ethnopharmacol 2011;134:703–10.
[24] Seo W-G, Pae H-O, Oh G-S, Chai K-Y, et al. Inhibitory effects of methanol extract of *Cyperus rotundus* rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7 cells. J Ethnopharmacol 2001;76:59–64.
[25] Sugimoto K, Sakamoto S, Nakagawa K, Hayashi S, et al. Suppression of inducible nitric oxide synthase expression and amelioration of lipopolysaccharide-induced liver injury by polyphenolic compounds in *Eucalyptus globulus* leaf extract. Food Chem 2011;125:442–6.
[26] Liu X, Wang J. Anti-inflammatory effects of iridoid glycosides fraction of *Folium syringae* leaves on TNBS-induced colitis in rats. J Ethnopharmacol 2011;133:780–7.
[27] El-Abhar HS, Hammad LNA, Gawad HSA. Modulating effect of ginger extract on rats with ulcerative colitis. J Ethnopharmacol 2008;118:367–72.
[28] Zhou Y-H, Yu J-P, Liu Y-F, Teng X-J, et al. Effect of *Ginkgo biloba* extract on inflammatory mediators (SOD, MDA, TNF-α, NF-κBp65, IL-6) in TNBS-induced colitis in rats. Mediators Inflamm 2006;2006:1–9.
[29] Abboud PA, Hake PW, Burroughs TJ, Odoms K, et al. Therapeutic effect of epigallocatechin-3-gallate in a mouse model of colitis. Eur J Pharm 2008;579:411–7.
[30] Park M-Y, Ji G, Sung M-K. Dietary kaempferol suppresses inflammation of dextran sulfate sodium–induced colitis in mice. Dig Dis Sci 2012;57:355–63.
[31] Edmunds SJ, Roy NC, Love DR, Laing WA. Kiwifruit extracts inhibit cytokine production by lipopolysaccharide-activated macrophages, and intestinal epithelial cells isolated from IL10 gene deficient mice. Cell Immunol 2011;270:70–9.
[32] Seo H-J, Huh J-E, Han J-H, Jeong S-J, et al. Polygoni Rhizoma inhibits inflammatory response through inactivation of nuclear factor-kappaB and mitogen activated protein kinase signaling pathways in RAW264.7 mouse macrophage cells. Phytother Res 2012;26:239–45.
[33] Jagtap AG, Shirke SS, Phadke AS. Effect of polyherbal formulation on experimental models of inflammatory bowel diseases. J Ethnopharmacol 2004;90:195–204.
[34] Romier-Crouzet B, Van De Walle J, During A, Joly A, et al. Inhibition of inflammatory mediators by polyphenolic plant extracts in human intestinal Caco-2 cells. Food Chem Toxicol 2009;47:1221–30.
[35] Larrosa M, González-Sarrías A, Yáñez-Gascón MJ, Selma MV, et al. Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A in a colitis rat model and the effect of colon inflammation on phenolic metabolism. J Nutr Biochem 2010;21:717–25.
[36] Kazłowska K, Hsu T, Hou C-C, Yang W-C, Tsai G-J. Anti-inflammatory properties of phenolic compounds and crude extract from *Porphyra dentata*. J Ethnopharmacol 2010;128: 123–30.
[37] Kim J-K, Oh S-M, Kwon H-S, Oh Y-S, et al. Anti-inflammatory effect of roasted licorice extracts on lipopolysaccharide-induced inflammatory responses in murine macrophages. Biochem Biophys Res Commun 2006;345:1215–23.
[38] Kwon KH, Murakami A, Hayashi R, Ohigashi H. Interleukin-1β targets interleukin-6 in progressing dextran sulfate sodium–induced experimental colitis. Biochem Biophys Res Commun 2005;337:647–54.
[39] Young D, Ibuki M, Nakamori T, Fan M, Mine Y. Soy-derived di- and tripeptides alleviate colon and ileum inflammation in pigs with dextran sodium sulfate–induced colitis. J Nutr 2012;142:363–8.
[40] Bassaganya-Riera J, Hontecillas R. CLA and n-3 PUFA differentially modulate clinical activity and colonic PPAR-responsive gene expression in a pig model of experimental IBD. Clin Nutr 2006;25:454–65.
[41] Bassaganya-Riera J, Reynolds K, Martino-Catt S, Cui Y, et al. Activation of PPAR γ and δ by conjugated linoleic acid mediates protection from experimental inflammatory bowel disease. Gastroenterology 2004;127:777–91.
[42] Evans NP, Misyak SA, Schmelz EM, Guri AJ, et al. Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPARγ. J Nutr 2010;140: 515–21.
[43] Reynolds CM, Loscher CE, Moloney AP, Roche HM. Cis-9, trans-11-conjugated linoleic acid but not its precursor

trans-vaccenic acid attenuate inflammatory markers in the human colonic epithelial cell line Caco-2. Br J Nutr 2008;100: 13–7.
[44] Lee Y, Thompson JT, Vanden Heuvel JP. 9E,11E-conjugated linoleic acid increases expression of the endogenous antiinflammatory factor, interleukin-1 receptor antagonist, in RAW 264.7 cells. J Nutr 2009;139:1861–6.
[45] Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev 2010;68:280–9.
[46] Sierra S, Lara-Villoslada F, Comalada M, Olivares M, Xaus J. Dietary fish oil n-3 fatty acids increase regulatory cytokine production and exert anti-inflammatory effects in two murine models of inflammation. Lipids 2006;41:1115–25.
[47] Kono H, Fujii H, Ogiku M, Tsuchiya M, et al. Enteral diets enriched with medium-chain triglycerides and N-3 fatty acids prevent chemically induced experimental colitis in rats. Transl Res 2010;156:282–91.
[48] Ibrahim A, Mbodji K, Hassan A, Aziz M, et al. Anti-inflammatory and anti-angiogenic effect of long chain n-3 polyunsaturated fatty acids in intestinal microvascular endothelium. Clin Nutr 2011;30:678–87.
[49] Li Q, Zhang Q, Wang M, Zhao S, et al. n-3 polyunsaturated fatty acids prevent disruption of epithelial barrier function induced by proinflammatory cytokines. Mol Immunol 2008;45:1356–65.
[50] Whiting CV, Bland PW, Tarlton JF. Dietary n-3 polyunsaturated fatty acids reduce disease and colonic proinflammatory cytokines in a mouse model of colitis. Inflamm Bowel Dis 2005;11:340–9.
[51] Borniquel S, Jansson EÅ, Cole MP, Freeman BA, Lundberg JO. Nitrated oleic acid up-regulates PPARγ and attenuates experimental inflammatory bowel disease. Free Radic Biol Med 2010;48:499–505.
[52] Camuesco D, Comalada M, Concha A, Nieto A, et al. Intestinal anti-inflammatory activity of combined quercitrin and dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, in rats with DSS-induced colitis. Clin Nutr 2006;25:466–76.
[53] Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol 2007;28:2826–32.
[54] Serpe L, Canaparo R, Daperno M, Sostegni R, et al. Solid lipid nanoparticles as anti-inflammatory drug delivery system in a human inflammatory bowel disease whole-blood model. Eur J Pharm Sci 2010;39:428–36.
[55] Hao W, Wong OY, Liu X, Lee P, et al. ω-3 fatty acids suppress inflammatory cytokine production by macrophages and hepatocytes. J Pediatr Surg 2010;45:2412–8.
[56] Schubert R, Kitz R, Beermann C, Rose MA, et al. Influence of low-dose polyunsaturated fatty acids supplementation on the inflammatory response of healthy adults. Nutrition 2007;23:724–30.
[57] McNamara RK, Jandacek R, Rider T, Tso P, et al. Omega-3 fatty acid deficiency increases constitutive pro-inflammatory cytokine production in rats: relationship with central serotonin turnover. Prostaglandins Leukot Essent Fatty Acids 2010;83:185–91.
[58] Ibrahim A, Aziz M, Hassan A, Mbodji K, et al. Dietary α-linolenic acid–rich formula reduces adhesion molecules in rats with experimental colitis. Nutrition 2012;28:799–802.
[59] Ohtsuka Y, Okada K, Yamakawa Y, Ikuse T, et al. ω-3 fatty acids attenuate mucosal inflammation in premature rat pups. J Pediatr Surg 2011;46:489–95.
[60] Grimstad T, Bjørndal B, Cacabelos D, Aasprong OG, et al. Dietary supplementation of krill oil attenuates inflammation and oxidative stress in experimental ulcerative colitis in rats. Scand J Gastroenterol 2012;47:49–58.
[61] Frias R, Ouwehand A, Spillmann T, Vankerckhoven V, et al. Effect of clinical and probiotic *Lactobacillus rhamnosus* strains on intestinal permeability and bacterial translocation in healthy and colitic rats. Food Res Int 2009;42:636–40.
[62] Pena JA, Rogers AB, Ge Z, Ng V, et al. Probiotic *Lactobacillus* spp. diminish *Helicobacter hepaticus*–induced inflammatory bowel disease in interleukin-10–deficient mice. Infect Immun 2005;73:912–20.
[63] Peran L, Camuesco D, Comalada M, Bailon E, et al. A comparative study of the preventative effects exerted by three probiotics, *Bifidobacterium lactis*, *Lactobacillus casei* and *Lactobacillus acidophilus*, in the TNBS model of rat colitis. J Appl Microbiol 2007;103:836–44.
[64] Schultz M, Veltkamp C, Dieleman LA, Grenther WB, et al. *Lactobacillus plantarum* 299V in the treatment and prevention of spontaneous colitis in interleukin-10–deficient mice. Inflamm Bowel Dis 2002;8:71–80.
[65] Madsen K, Cornish A, Soper P, McKaigney C, et al. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. Gastroenterology 2001;121:580–91.
[66] Rachmilewitz D, Katakura K, Karmeli F, Hayashi T, et al. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. Gastroenterology 2004;126:520–8.
[67] Imaoka A, Shima T, Kato K, Mizuno S, et al. Anti-inflammatory activity of probiotic *Bifidobacterium*: enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. World J Gastroenterol 2008;28:2511–6.
[68] Drouault-Holowacz S, Foligné B, Dennin V, Goudercourt D, et al. Anti-inflammatory potential of the probiotic dietary supplement Lactibiane Tolérance: in vitro and in vivo considerations. Clin Nutr 2006;25:994–1003.
[69] Abdin AA, Saeid EM. An experimental study on ulcerative colitis as a potential target for probiotic therapy by *Lactobacillus acidophilus* with or without "olsalazine". J Crohns Colitis 2008;2:296–303.
[70] Lorea Baroja M, Kirjavainen PV, Hekmat S, Reid G. Anti-inflammatory effects of probiotic yogurt in inflammatory bowel disease patients. Clin Exp Immunol 2007;149:470–9.
[71] Herías MV, Koninkx JFJG, Vos JG, Huis in't Veld JHJ, van Dijk JE. Probiotic effects of *Lactobacillus casei* on DSS-induced ulcerative colitis in mice. Int J Food Microbiol 2005;103: 143–55.
[72] Dalmasso G, Cottrez F, Imbert V, Lagadec P, et al. *Saccharomyces boulardii* inhibits inflammatory bowel disease by trapping T cells in mesenteric lymph nodes. Gastroenterology 2006;131:1812–25.
[73] Matsumoto S, Hara T, Hori T, Mitsuyama K, et al. Probiotic *Lactobacillus*-induced improvement in murine chronic inflammatory bowel disease is associated with the down-regulation of pro-inflammatory cytokines in lamina propria mononuclear cells. Clin Exp Immunol 2005;140: 417–26.
[74] O'Mahony L, Feeney M, O'Halloran S, Murphy L, et al. Probiotic impact on microbial flora, inflammation and tumour development in IL-10 knockout mice. Aliment Pharmacol Ther 2001;15:1219–25.
[75] Khokhlova EV, Smeianov VV, Efimov BA, Kafarskaia LI, et al. Anti-inflammatory properties of intestinal *Bifidobacterium* strains isolated from healthy infants. Microbiol Immunol 2012;56:27–39.
[76] Takata K, Kinoshita M, Okuno T, Moriya M, et al. The lactic acid bacterium *Pediococcus acidilactici* suppresses autoimmune encephalomyelitis by inducing IL-10–producing regulatory T cells. PLoS One 2011;6:e27644.
[77] Xia Y, Chen H-Q, Zhang M, Jiang Y-Q, et al. Effect of *Lactobacillus plantarum* LP-Onlly on gut flora and colitis in

interleukin-10 knockout mice. J Gastroenterol Hepatol 2011;26:405–11.
[78] Sabit H, Farouk A, Said O, Yehia M, Bishr A. Molecular characterization of *Bifidobacteria* and *Lactobacillus* and their role in modulating immune system and alleviating ulcerative colitis in mice. Global J Mol Sci 2011;6:09–14.
[79] Duary R, Bhausaheb M, Batish V, Grover S. Anti-inflammatory and immunomodulatory efficacy of indigenous probiotic *Lactobacillus plantarum* Lp91 in colitis mouse model. Mol Biol Rep 2012;39:4765–75.
[80] Rodríguez-Cabezas ME, Gálvez J, Camuesco D, Lorente MD, et al. Intestinal anti-inflammatory activity of dietary fiber (*Plantago ovata* seeds) in HLA-B27 transgenic rats. Clin Nutr 2003;22:463–71.
[81] Bassaganya-Riera J, DiGuardo M, Viladomiu M, de Horna A, Sanchez S, Einerhand AW, et al. Soluble fibers and resistant starch ameliorate disease activity in interleukin-10–deficient mice with inflammatory bowel disease. J Nutr 2011;141:1318–25.
[82] Magri LDP, Batista LM, Almeida ABA, Farias-Silva E, et al. Dietary fibers prevent ethanol and nonsteroidal anti-inflammatory drug–induced gastric mucosal damage in rats. Nutr Res 2007;27:109–12.
[83] Kanauchi O, Iwanaga T, Andoh A, Araki Y, et al. Dietary fiber fraction of germinated barley foodstuff attenuated mucosal damage and diarrhea, and accelerated the repair of the colonic mucosa in an experimental colitis. J Gastroenterol Hepatol 2001;16:160–8.
[84] Rose DJ, DeMeo MT, Keshavarzian A, Hamaker BR. Influence of dietary fiber on inflammatory bowel disease and colon cancer: importance of fermentation pattern. Nutr Rev 2007;65:51–62.
[85] Lim BO, Lee SH, Park DK, Choue RW. Effect of dietary pectin on the production of immunoglobulins and cytokines by mesenteric lymph node lymphocytes in mouse colitis induced with dextran sulfate sodium. Biosci Biotechnol Biochem 2003;67:1706–12.
[86] Ye MB, Lim BO. Dietary pectin regulates the levels of inflammatory cytokines and immunoglobulins in interleukin-10 knockout mice. J Agric Food Chem 2010;58: 11281–6.
[87] Pouillart PR, Dépeint F, Abdelnour A, Deremaux L, et al. Nutriose, a prebiotic low-digestible carbohydrate, stimulates gut mucosal immunity and prevents TNBS-induced colitis in piglets. Inflamm Bowel Dis 2010;16:783–94.
[88] Faghfoori Z, Navai L, Shakerhosseini R, Somi MH, et al. Effects of an oral supplementation of germinated barley foodstuff on serum tumour necrosis factor-α, interleukin-6 and -8 in patients with ulcerative colitis. Ann Clin Biochem 2011;48:233–7.
[89] Komiyama Y, Andoh A, Fujiwara D, Ohmae H, et al. New prebiotics from rice bran ameliorate inflammation in murine colitis models through the modulation of intestinal homeostasis and the mucosal immune system. Scand J Gastroenterol 2011;46:40–52.
[90] Komiyama Y, Mitsuyama K, Masuda J, Yamasaki H, et al. Prebiotic treatment in experimental colitis reduces the risk of colitic cancer. J Gastroenterol Hepatol 2011;26:1298–308.
[91] Azuma K, Osaki T, Wakuda T, Ifuku S, et al. Beneficial and preventive effect of chitin nanofibrils in a dextran sulfate sodium–induced acute ulcerative colitis model. Carbohydr Polym 2012;87:1399–403.
[92] Rousseaux C, Lefebvre B, Dubuquoy L, Lefebvre P, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator–activated receptor-γ. J Exp Med 2005;201:1205–15.
[93] Desreumaux P, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid—new evidence. Aliment Pharmacol Ther 2006;24:2–9.
[94] Horváth K, Varga C, Berkó A, Pósa A, et al. The involvement of heme oxygenase-1 activity in the therapeutic actions of 5-aminosalicylic acid in rat colitis. Eur J Pharmacol 2008;581: 315–23.
[95] Tozaki H, Odoriba T, Okada N, Fujita T, et al. Chitosan capsules for colon-specific drug delivery: enhanced localization of 5-aminosalicylic acid in the large intestine accelerates healing of TNBS-induced colitis in rats. J Control Release 2002;82:51–61.
[96] Pertuit D, Moulari B, Betz T, Nadaradjane A, et al. 5-Amino salicylic acid bound nanoparticles for the therapy of inflammatory bowel disease. J Control Release 2007;123: 211–8.
[97] Brown JB, Lee G, Managlia E, Grimm GR, et al. Mesalamine inhibits epithelial β-catenin activation in chronic ulcerative colitis. Gastroenterology 2010;138:595–605.e593.
[98] Mura C, Nácher A, Merino V, Merino-Sanjuan M, et al. *N*-succinyl-chitosan systems for 5-aminosalicylic acid colon delivery: in vivo study with TNBS-induced colitis model in rats. Int J Pharm 2011;416:145–54.
[99] Ancha HR, Kurella RR, McKimmey CC, Lightfoot S, HartY RF. Luminal antioxidants enhance the effects of mesalamine in the treatment of chemically induced colitis in rats. Exp Biol Med 2008;233:1301–8.
[100] Leung DYM, Bloom JW. Update on glucocorticoid action and resistance. J Allergy Clin Immunol 2003;111:3–22.
[101] Joo K, Lee Y, Choi D, Han J, et al. An anti-inflammatory mechanism of taurine conjugated 5-aminosalicylic acid against experimental colitis: taurine chloramine potentiates inhibitory effect of 5-aminosalicylic acid on IL-1β–mediated NFκB activation. Eur J Pharmacol 2009;618:91–7.
[102] Bautzová T, Rabišková M, Béduneau A, Pellequer Y, Lamprechtr A. Bioadhesive pellets increase local 5-aminosalicylic acid concentration in experimental colitis. Eur J Pharm Biopharm 2012;81:379–85.
[103] Aguzzi C, Ortega A, Bonferoni MC, Sandri G, et al. Assessement of anti-inflammatory properties of microspheres prepared with chitosan and 5-amino salicylic acid over inflamed Caco-2 cells. Carbohydr Polym 2011;85:638–44.
[104] Gorgulu S, Yagci G, Kaymakcioglu N, Özkara M, et al. Hyperbaric oxygen enhances the efficiency of 5-aminosalicylic acid in acetic acid–induced colitis in rats. Dig Dis Sci 2006;51:480–7.
[105] Dhaneshwar SS, Chail M, Patil M, Naqvi S, Vadnerkar G. Colon-specific mutual amide prodrugs of 4-aminosalicylic acid for their mitigating effect on experimental colitis in rats. Eur J Med Chem 2009;44:131–42.
[106] Stolfi C, Fina D, Caruso R, Caprioli F, et al. Cyclooxygenase-2–dependent and –independent inhibition of proliferation of colon cancer cells by 5-aminosalicylic acid. Biochem Pharmacol 2008;75:668–76.
[107] Manuela GN. Immune dysfunction in inflammatory bowel disease. Transl Res 2007;149:173–86.
[108] Dionne S, D'Agata DD, Hiscott J, Vanounou T, Seidman EG. Colonic explant production of IL-1 and its receptor antagonist is imbalanced in inflammatory bowel disease (IBD). Clin Exp Immunol 1998;112:435–42.
[109] Malek R, Borowicz KK, Jargiello M, Czuczwar SJ. Role of nuclear factor B in the central nervous system. Pharmacol Rep 2007;59:25–33.
[110] Zhang D, Cheng L, Huang X, Shi W, et al. Tetrandrine ameliorates dextran-sulfate-sodium–induced colitis in mice through inhibition of nuclear factor-κB activation. Int J Colorectal Dis 2009;24:5–12.
[111] Neurath MF, Pettersson S, Meyer zum Buschenfelde KH, Strober W. Local administration of antisense phosphorothioate oligonucleotides to the p65 subunit of NF-kappa B abrogates established experimental colitis in mice. Nat Med 1996;9:998–1004.

[112] Atreya R, Neurath MF. New therapeutic strategies for treatment of inflammatory bowel disease. Mucosal Immunol 2008;1:175–82.
[113] An MJ, Cheon JH, Kim SW, Park JJ, et al. Bovine colostrum inhibits nuclear factor κB–mediated proinflammatory cytokine expression in intestinal epithelial cells. Nutr Res 2009;29:275–80.
[114] Park Y-K, Rasmussen HE, Ehlers SJ, Blobaum KR, et al. Repression of proinflammatory gene expression by lipid extract of Nostoc commune var sphaeroides Kützing, a blue-green alga, via inhibition of nuclear factor-κB in RAW 264.7 macrophages. Nutr Res 2008;28:83–91.
[115] Vanden Berghe W, Vermeulen L, Delerive P, De Bosscher K, Staels B, Haegerman G. A paradigm for gene regulation: Inflammation, NF-kappaB and PPAR. Adv Exp Med Biol 2003;544:181–96.
[116] Talero E, Sánchez-Fidalgo S, de la Lastra CA, Illanes M, et al. Acute and chronic responses associated with adrenomedullin administration in experimental colitis. Peptides 2008;29:2001–12.
[117] Roy PK, Rashid F, Bragg J, Ibdah JA. Role of the JNK signal transduction pathway in inflammatory bowel disease. World J Gastroenterol 2008;14:200–2.
[118] Mora A, Payá M, Ríos JL, Alcaraz MJ. Structure-activity relationships of polymethoxyflavones and other flavonoids as inhibitors of non-enzymic lipid peroxidation. Biochem Pharmacol 1990;40:793–7.
[119] Erlund I, Kosonen T, Alfthan G, Mäenpää J, et al. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. Eur J Clin Pharmacol 2000;56: 545–53.
[120] Gálvez J, Cruz T, Crespo E, Ocete MA, et al. Rutoside as mucosal protective in acetic acid–induced rat colitis. Planta Med 1997;63:409,414.
[121] Dryden GW, Song M, McClain C. Polyphenols and gastrointestinal diseases. Curr Opin Gastroenterol 2006;22: 165–70 [110.1097/1001.mog.0000208463.0000269266.0000208468c].
[122] Soobrattee MA, Neergheen VS, Luximon-Ramma A, Aruoma OI, Bahorun T. Phenolics as potential antioxidant therapeutic agents: mechanism and actions. Mutat Res/Fundam Mol Mech Mutagen 2005;579:200–13.
[123] Yang F, Oz HS, Barve S, de Villiers WJS, et al. The green tea polyphenol (–)-epigallocatechin-3-gallate blocks nuclear factor-κB activation by inhibiting IκB kinase activity in the intestinal epithelial cell line IEC-6. Mol Pharmacol 2001;60: 528–33.
[124] Ran ZH, Chen C, Xiao SD. Epigallocatechin-3-gallate ameliorates rats colitis induced by acetic acid. Biomed Pharmacother 2008;62:189–96.
[125] Lu J, Ho C-T, Ghai G, Chen KY. Differential effects of theaflavin monogallates on cell growth, apoptosis, and Cox-2 gene expression in cancerous versus normal cells. Cancer Res 2000;60:6465–71.
[126] Peng G, Dixon DA, Muga SJ, Smith TJ, Wargovich MJ. Green tea polyphenol (–)-epigallocatechin-3-gallate inhibits cyclooxygenase-2 expression in colon carcinogenesis. Mol Carcinog 2006;45:309–19.
[127] Lin Y-L, Lin J-K. (–)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of transcription factor nuclear factor-κB. Mol Pharmacol 1997;52:465–72.
[128] Bengmark S. Bioecological control of inflammatory bowel disease. Clin Nutr 2007;26:169–81.
[129] Park J-Y, Kawada T, Han I-S, Kim B-S, et al. Capsaicin inhibits the production of tumor necrosis factor α by LPS-stimulated murine macrophages, RAW 264.7: a PPARγ ligand-like action as a novel mechanism. FEBS Lett 2004;572:266–70.
[130] Kruidenier L, Verspaget HW. Oxidative stress as a pathogenic factor in inflammatory bowel disease—radicals or ridiculous? Aliment Pharmacol Ther 2002;16:1997–2015.
[131] Cross RK, Wilson KT. Nitric oxide in inflammatory bowel disease. Inflamm Bowel Dis 2003;9:179–89.
[132] Beckman KB, Ames BN. Oxidative decay of DNA. J Biol Chem 1997;272:19633–6.
[133] Shiratora Y, Aoki S, Takada H, Kiriyama H, et al. Oxygen-derived free radical generating capacity of polymorphonuclear cells in patients with ulcerative colitis. Digestion 1989;44:163–71.
[134] Islam MS, Murata T, Fujisawa M, Nagasaka R, et al. Anti-inflammatory effects of phytosteryl ferulates in colitis induced by dextran sulphate sodium in mice. Br J Pharmacol 2008;154:812–24.
[135] Mårtensson J, Jain A, Meister A. Glutathione is required for intestinal function. Proc Natl Acad Sci 1990;87:1715–9.
[136] Khan SG, Katiyar SK, Agarwal R, Mukhtar H. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. Cancer Res 1992;52:4050–2.
[137] Parfitt K, editor. Martindale—the complete drug reference, 32nd ed. United Kingdom: Pharmaceutical Press; 1999. p. 1199.
[138] Nobilis M, Vybíralová Z, Sládková K, Lísa M, et al. High-performance liquid-chromatographic determination of 5-aminosalicylic acid and its metabolites in blood plasma. J Chromatogr A 2006;1119:299–308.
[139] Lakhan S, Kirchgessner A. Neuroinflammation in inflammatory bowel disease. J Neuroinflammation 2010;7:37.
[140] Paul G, Bataille F, Obermeier F, Bock J, Klebl F, Strauch U, et al. Analysis of intestinal haem-oxygenase-1 (HO-1) in clinical and experimental colitis. Clin Exp Immunol 2005;140:547–55.
[141] Sanovic S, Lamb D, Blennerghassett M. Damage to the enteric nervous system in experimental colitis. Am J Pathol 1999;155:1051–7.
[142] Collier-Hyams L, Neish A. Intestinal epithelial barrier and mucosal immunity. Cell Mol Life Sci 2005;62:1339–48.
[143] Fellermann K, Wehkamp J, Herrlinger KR, Stange EF. Crohn's disease: a defensin deficiency syndrome? Eur J Gastroenterol Hepatol 2003;15:627–34.
[144] Yan F, Polk DB. Probiotic bacterium prevents cytokine-induced apoptosis in intestinal epithelial cells. J Biol Chem 2002;277:50959–65.
[145] Candela M, Perna F, Carnevali P, Vitali B, et al. Interaction of probiotic *Lactobacillus* and *Bifidobacterium* strains with human intestinal epithelial cells: adhesion properties, competition against enteropathogens and modulation of IL-8 production. Int J Food Microbiol 2008;125:286–92.
[146] Geier MS, Butler RN, Howarth GS. Inflammatory bowel disease: current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and synbiotics. Int J Food Microbiol 2007;115:1–11.
[147] LeBlanc J, Carmen SD, Miyoshi A, Azevedo V, et al. Use of superoxide dismutase and catalase producing lactic acid bacteria in TNBS induced Crohn's disease in mice. J Biotechnol 2011;15:287–93.
[148] Hendrickson B, Gokhale R, Cho J. Clinical aspects and pathophysiology of inflammatory bowel disease. Clin Microbiol Rev 2002:79–94.
[149] Hyun J, Mayer L. Mechanisms underlying inflammatory bowel disease. Drug Discov Today Dis Mech 2006;3:457–62.
[150] Neuman M, Nanau R. Inflammatory bowel disease: role of diet, microbiota, life style. Transl Res 2012;160:29–44.
[151] DeVroey B, Cassan CD, Gower-Rousseau C, Colombel J. Editorial: antibiotics earlier, IBD later? Am J Gastroenterol 2010;105:2693–6.

[152] Koretz RL. Immunonutrition: can you be what you eat? Curr Opin Gastroenterol 2003;19:134–9.
[153] Esteve-Comas M, Ramírez M, Fernández-Bañares F, Abad-Lacruz A, et al. Plasma polyunsaturated fatty acid pattern in active inflammatory bowel disease. Gut 1992;33: 1365–9.
[154] Serhan CN, Clish CB, Brannon J, Colgan SP, et al. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2–nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med 2000;192:1197–204.
[155] Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway. N Engl J Med 1990;323:645–55.
[156] Calder PC. Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases. Mol Nutr Food Res 2008;52:885–97.
[157] Andersen V, Olsen A, Carbonnel F, Tjønneland A, Vogel U. Diet and risk of inflammatory bowel disease. Dig Liver Dis 2012;44:185–94.
[158] Shoda R, Matsueda K, Yamato S, Umeda N. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. Am J Clin Nutr 1996;63:741–5.
[159] Alzoghaibi MA, Walsh SW, Willey A, Fowler Iii AA, Graham MF. Linoleic acid, but not oleic acid, upregulates the production of interleukin-8 by human intestinal smooth muscle cells isolated from patients with Crohn's disease. Clin Nutr 2003;22:529–35.
[160] Shores D, Binion D, Freeman B, Baker P. New insights into the role of fatty acids in the pathogenesis and resolution of inflammatory bowel disease. Inflamm Bowel Dis 2011;17: 2192–204.
[161] Zhao G, Etherton T, Martin K, West S, et al. Dietary α-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr 2004;134:2291–7.
[162] Magee P, Pearson S, Whittingham-Dowd J, Allen J. PPARγ as a molecular target of EPA anti-inflammatory activity during TNF-α–impaired skeletal muscle cell differentiation. J Nutr Biochem 2012 [in press].
[163] Kawashima A, Harada T, Imada K, Yano T, Mizuguchi K. Eicosapentaenoic acid inhibits interleukin-6 production in interleukin-1beta–stimulated C6 glioma cells through peroxisome proliferator–activated receptor-gamma. Prostag Leukot Essent Fatty Acids 2008;79:59–65.
[164] Draper E, Reynolds C, Canavan M, Mills K, et al. Omega-3 fatty acids attenuate dendritic cell function via NF-kappaB independent of PPARgamma. J Nutr Biochem 2011;22:784–90.