Nutritional Interventions Using Functional Foods and Nutraceuticals to Improve Inflammatory Bowel Disease

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ABSTRACT The gastrointestinal tract, the second largest organ in the body, plays an important role in nutrient and mineral intake through the intestinal barrier. Dysfunction of intestinal permeability and related disorders commonly occur in patients with inflammatory bowel disease (IBD), one of the health problems in the Western societies that are considered to be mainly due to the Western diet. Although the exact etiology of IBD has not been elucidated, environmental and genetic factors may be involved in its pathogenesis. Many synthetic or biological drugs, such as 5-aminosalicylic acid corticosteroids as anti-inflammatory drugs, have been used clinically to treat IBD. However, their long-term use exhibits some adverse health consequences. Therefore, many researchers have devised alternative therapies to overcome this problem. Many studies have revealed that some functional nutrients in nature can relieve gastrointestinal inflammation by controlling proinflammatory cytokines. In this study, we review the ability of functional nutraceuticals such as phytochemicals, fatty acids, and bioactive peptides in improving IBD by regulating its underlying pathogenic mechanisms.

KEYWORDS: • *functional foods* • *nutraceuticals* • *inflammatory bowel disease*

INTRODUCTION

INFLAMMATORY BOWEL DISEASE (IBD), a chronic gastrointestinal disease characterized by recurrent inflammation in the intestine and severe mucosal damage, is generally divided into two categories: ulcerative colitis (UC) and Crohn's disease (CD). These symptoms include diarrhea, nausea, abdominal pain, rectal bleeding, and weight loss.¹ Recent research has shown a correlation between nutrition and risk of developing IBD in countries with a fat-and-protein-rich diet similar to that observed in Western countries.² We speculate that genetic susceptibility, percentage of intestinal microorganisms, and types of nutrition play important roles in the pathogenesis of IBD.³

Nutritional interventions aimed at potentially reducing nutritional risk are attracting attention as a treatment method for IBD that induces prolonged disease relief.⁴ Recent studies suggest that fruits, vegetables, probiotics, and fiber can significantly decrease the symptoms of IBD through anti-inflammatory effects.^{5–9} In contrast, because high-fat foods and high-carbohydrate foods are known to contribute to the development of IBD, limiting the intake of these foods helps improve IBD.^{10,11} Functional foods and bioactive natural compounds have been key research topics to provide

potential treatments for improving IBD. Several groups have suggested that active materials derived from various plants exert potent anti-inflammatory effects against IBD through various mechanisms.^{12–15} These types of research will continuously provide much evidence and scientific rationale about the use of a healthy diet or functional foods to improve or ameliorate the symptoms of IBD. Therefore, in this study we review the beneficial effects of various dietary nutrients as a treatment method for improving IBD.

CHARACTERISTICS OF UC AND CD

Both UC and CD share a common symptom but have different histopathological and symptomatic characteristics. UC is characterized by mucosal or submucosal inflammation, usually in the rectum and sometimes in the colon, with symptoms of abdominal pain, diarrhea, and bleeding. CD can occur in the gastrointestinal tract and cause intestinal granuloma, fistula, and stenosis, but is caused by inflammation of the intestinal tract and colon that leads to abdominal pain, diarrhea, fever, appetite, weight loss, and intermittent anal fissures. Although the pathogenesis of IBD has not been clarified to date, various dietary, immunological, environmental, genetic, and microbial factors have been identified as causes.¹⁴ Complex interactions of genetic, environmental, microbiological, and immunological factors can simultaneously induce various cytokines, activating the mucosal immune responses.¹⁵ Cytokines, which are mainly produced by immune cells, transmit specific signals that

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interact with cells, causing local and systemic inflammatory reactions. Unlike healthy individuals, patients with IBD develop imbalances between intestinal homeostasis and inflammatory cytokines that induce an unusual increase in the proinflammatory cytokine activity in the mucosa, dysfunction of the epithelial barrier, and damage to one's intestinal permeability.¹⁶

POSSIBLE MOLECULAR TARGETS IN IBD

Tumor necrosis factor- α

A proinflammatory cytokine, tumor necrosis factor alpha (TNF- α), which is primarily secreted by activated macrophages, is elevated in patients with IBD.¹⁷ The increased production of TNF- α triggers mucosal inflammation, and causes the impairment of the intestinal barrier by malfunctioning tight junctions as well as cell death of intestinal epithelial cells (IECs).¹⁸ The excess level of TNF- α initiates a positive feedback loop by causing the secretion of interleukin (IL)-1 β and IL-6, which are chiefly produced by leukocytes, mast cells, macrophages, and neutrophils.^{19,20} IL-6 activates Th17 and Th2 responses, which aggravate the inflammation. This cytokine cascade leads to harmful effects on the barrier function.

Nuclear factor-kappa B

Nuclear factor-kappa B (NF- κ B) plays a key role in mediating inflammation by regulating the expression of many proinflammatory genes.²¹ NF- κ B signaling is dysregulated in IBD, which causes excessive inflammation in IBD patients. Among canonical or noncanonical, the activation of the canonical NF- κ B pathway is observed in IBD and related to the acute expression of cyclooxygenase 2 (COX-2), IL-1 β , and IL-6.^{22,23}

Interleukin-6

IL-6 is found to increase in the inflammatory tissues and serum of patients with IBD. A humanized monoclonal antibody (tocilizumab) against IL-6, approved for the treatment of rheumatic conditions, was reportedly successful in case reports of IBD.²⁴ However, according to some results of siplizumab treatment in patients with IBD, the rate of intestinal perforation appeared to be relatively increased.²⁵ To date, other antibodies against IL-6 have been developed and studied in preclinical studies but have not yet been evaluated in clinical trials.

Interleukin-22

IL-22 is reportedly more highly expressed in patients with CD.²⁶ IL-22 has a protective role, but induces inflammation under certain conditions.²⁷ A previous study reported that IL-22-mediated gene therapy can inhibit inflammatory responses and mitigate tissue damage.²⁸ In addition, the clinical relevance of IL-22 for IBD has been well described. Mucosal healing, the current therapeutic target for IBD, can be enhanced by IL-22. IL-22 increases the expression level

of MUC1, a core protein of the mucus layer.^{29,30} Patients with IBD lacking IL-1 β 0R2, an IL-22 receptor, do not express the glycosylated protein MUC1.³¹ Therefore, since IL-22 is linked to the main function of the intestinal barrier, future studies are needed to confirm its role in IBD and its therapeutic potential.

CURRENT CLINICAL TREATMENTS FOR CURING PATIENTS WITH IBD

Since we do not know the exact underlying pathogenic mechanism of IBD, there is currently no effective treatment for IBD. The current goal of IBD treatment is to significantly reduce the inflammation that causes symptoms and signs to achieve symptomatic relief as well as long-term remission and a decreased risk of complications.

Anti-inflammatory drugs

Anti-inflammatory drugs are the first to be prescribed clinically for the treatment of IBD. These drugs are usually corticosteroids and aminosalicylates such as balsalazide (Colazal), mesalamine (Asacol HD, Delzicol, others), and olsalazine (Dipentum).³² These drugs improve the symptoms of IBD by blocking or reducing proinflammatory cytokines. These drugs are differently prescribed depending on the affected colon site.

Immune system suppressors

These drugs work by suppressing the immune response to released inflammatory substances in the intestines. Interestingly, a combination of these drugs works better than a single drug for some people. These immunosuppressant drugs are cyclosporine (Gengraf, Neoral, Sandimmune), azathioprine (Azasan, Imuran), mercaptopurine (Purinethol, Purixan), and methotrexate (Trexall).³³

Biologics

The use of biological drugs derived from living biological resources have become widespread and treat IBD by neutralizing a protein produced by the immune system. The representative biologics for IBD are TNF- α inhibitors such as infliximab (Remicade), adalimumab (Humira), and golimumab (Simponi). Other types of therapeutic biologics such as natalizumab (Tysabri) against the cell adhesion molecule α 4-integrin, vedolizumab (Entyvio) against integrins, and ustekinumab (Stelara), an IL-12 and IL-23 antagonist, are approved for treating IBD.³⁴

Antibiotics

In addition to other medications or cases of infection, antibiotics such as ciprofloxacin (Cipro) and metronidazole (Flagyl) are generally prescribed in CD occurring around the anus.³⁵

FUNCTIONAL NUTRACEUTICALS FOR IMPROVING IBD

Despite providing some temporary symptomatic relief, the current drugs may cause serious side effects.³⁶ Biologics, which have recently become the focus of treatment for IBD, are expensive compared with other drugs. Therefore, we will review alternative IBD therapies by utilizing natural products, which are relatively safe and inexpensive.

Nutraceuticals means foods or food supplements manufactured or processed to potentiate functional bioactive ingredients with pharmacological properties. Molecular, biological, and cellular mechanisms of natural bioactive compounds for nutraceuticals have been continuously elucidated. Some researchers have reported that various substances, the main components of functional foods capable of improving IBD, can alleviate IBD symptoms by suppressing the inflammatory pathways⁵⁻⁷ (Table 1).

Phytochemicals

Phytochemicals are generally derived from the primary and secondary metabolisms in plants as part of their survival mechanisms against pathogens. These chemicals possess important physiological functions against oxidative stress and the inflammatory response. Phytochemicals can be classified into major categories, such as alkaloids, and polyphenols, which include flavonoids and phenolic acids.

Anthocyanin-rich bilberry extract decreases the expression levels of IFN- γ and TNF- α but increases those of the immunoregulatory cytokine IL-10 and Th17 cell-specific cytokine IL-22.³⁷ Kaempferol decreased IL-6, IL-1 β , TNF- α , inducible nitric oxide synthase (iNOS), COX-2 levels, nitric oxide (NO), prostaglandin E2 (PGE2), and colonic mucosa myeloperoxidase (MPO) activity in colitis mice model treated with dextran sodium sulfate (DSS).³⁸ Quercetin reduced MPO activity, increased glutathione (GSH) content, and reduced colon impairment in a colitis rat model treated with acetic acid.³⁹ Isoquercitrin downregulated COX-2 and iNOS expressions in a DSS-induced acute colitis model in rats.⁴⁰ Apigenin significantly decreased iNOS, COX-2, IL-1 β , and TNF- α production in DSS-induced colitis in mice.⁴¹

Hesperidin showed reduced MPO activity and IL-6 levels.⁴² Poncirin and its metabolite ponciretin improved the symptom of colitis in mice treated with 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) by reducing NF- κ B activation.⁴³ Myricetin contributes to weight loss, improving histological scores, and the suppression of NO, MPO, IL-1 β , and IL-6 but enhances activities of superoxide dismutase and glutathione peroxidase.⁴⁴ Naringenin increased the content of colonic mucus and reduced interferon (INF)- γ , IL-1 β , IL-6, PGE2, NO, and macrophage inflammatory protein in a colitis mouse model.^{45,46} Naringin ameliorated colonic mucosal damage and ulcer lesions by increasing superoxide dismutase and GSH levels.⁴⁷

Apple polyphenols significantly reduced the mRNA expression of IL-1 β and TNF- α in a colitis mouse model.⁴⁸ Resveratrol, a representative polyphenol found in red grapes

and several berry species, has modulatory effects on the oxidative process and inflammatory pathways as well as antiaging effects.⁴⁹ A previous study reported that resveratrol decreased NF- κ B activation, and downregulated activation of STAT3 in DSS-induced mouse.⁵⁰ A recent study demonstrated that resveratrol ameliorated inflammation and significantly reduced expression levels of TNF- α and NF- κ B in patients with UC compared with the control group.⁵¹

Curcumin, the principal curcuminoid derived from turmeric, has been used medically in some Eastern Asian countries. A previous study demonstrated that curcumin improved the tissue status of the colon by inhibiting STAT3 activity and decreasing TNF- α and IL-1 β expressions.⁵² Curcumin also significantly inhibited the activation of NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome by DSS treatment and ameliorate DSS-induced colitis in mice.⁵³

Sophocarpine and sophoridine, isolated from *Sophora alopecuroides*, have been used as traditional Chinese medicine for treating rheumatism.^{54,55} Studies on DSS-induced murine colitis showed that sophocarpine (15, 30, or 60 mg/kg body weight) decreased levels of IL-1 β , IL-6, and colonic MPO activity, and improved the symptom of DSS-induced colitis.⁵⁶

Berberine, a well-known representative isoquinoline alkaloid that is isolated from *Coptis chinensis* and *Phellodendron chinense*, reportedly can protect against colitis by controlling the gut microbiota, the innate and adaptive immune responses, and the function of the intestinal barrier.⁵⁷ Another study demonstrated that berberine significantly decreased levels of IFN- γ , IL-17, IL-6, IL-1 β , and TNF- α in the local colon but increased IL-22 levels.⁵⁸

Isatin (6 and 25 mg/kg of body weight), obtained from *Isatis tinctoria*, protects against TNBS-induced gut mucosa injury in rats by reducing the expression level of COX-2, PGE2, and TNF- α and enhancing IL-10 levels.⁵⁹ Tryptanthrin, which is obtained from *Polygonum tinctorium*, can treat inflammation, allergy, and cancer.⁶⁰ Several studies have revealed that tryptanthrin treatment significantly attenuated colonic mucosal injury by decreasing the production of PGE2, TNF- α , and NO in the TNF- α /NF- κ B and IL-6/STAT3 signaling pathways in a colitis model treated with DSS.^{61,62}

A previous study has demonstrated that caffeine, a natural xanthine alkaloid, relieved colitis symptoms by decreasing the expression level of chitinase 3-like 1 in the IECs.⁶³

Ginsenoside Rg1 and ginsenoside Rh1 could inhibit colon shortening, MPO activity, the expression levels of IL-1 β , IL-17, TNF- α , and restores the imbalance of Th17/Treg.⁶⁴ Ginsenoside Rd alleviates colon inflammatory symptoms by inhibiting the NLRP3 inflammasome in a dose-dependent manner.⁶⁵ Ginsenoside Re suppressed NF- κ B activity and antagonized the decrease of intestinal barrier function in IBD.⁶⁶ Astragaloside IV, a cycloartane triterpene saponin, stimulated nuclear translocation of β -catenin and induced mucosal healing in colitis by regulating energy metabolism.⁶⁷ Saponins improve intestinal health by inhibiting excessive inflammation by interaction with inflammatory pathways such as the NF- κ B, MAPK, and TLR4 pathways.

TABLE 1. ROLE OF EACH NUTRITIONAL AGENT AGAINST INFLAMMATORY BOWEL DISEASE

<i>Material</i>	<i>Main compound/ingredient</i>	<i>Species</i>	<i>Sample size</i>	<i>Effect size</i>	<i>Treatment</i>	<i>Mode of action</i>	<i>References</i>
Phytochemical	Anthocyanin-rich bilberry extract Kaempferol	Colon biopsies of UC patients	11 patients	Bilberry 160 g	Oral intake for 6 weeks	Decrease IFN- γ and TNF- α Increase IL-10, IL17, and IL-22	37
		DSS-induced colitis mice	10 animals/group	Kaempferol 0.1 and 0.3%	Oral intake for 2 weeks	Decrease TNF- α , IL-6, IL-1 β , iNOS, COX-2 levels, colonic mucosa MPO activity, NO, and PGE2	38
		3% acetic acid-induced CD rat	6 animals/group	Quercetin 50 or 100 mg/kg	Oral intake for 5 days	Reduce MPO activity Increase GSH	39
	Isoquercitrin	5% DSS-induced colitis rat	8 animals/group	Isoquercitrin 1 or 10 mg/kg per day	Oral intake for 2 weeks	Downregulate COX-2 and iNOS	40
		3% DSS-induced chronic colitis mice	10 animals/group	Apigenin 0.1%	Oral intake for 5 days	Decrease iNOS, COX-2, MMP3, IL-1 β , and TNF- α	41
	Hesperidin	5% DSS-induced chronic colitis mice	10 animals/group	Hesperidin 10, 40, or 80 mg/kg	Oral intake for 1 week	Reduce MPO activity and IL-6	42
	Poncirin, ponciretin	2.5% TNBS-induced colitis mice	6 animal/group	Poncirin (10 or 20 mg/kg), ponciretin (10 or 20 mg/kg)	Oral intake for 3 days	Reduce MPO activity and NF- κ B activation	43
	Myricetin	5% DSS-induced chronic colitis mice	8 animals/group	Myricetin 200, 100 or 50 mg/kg	Oral intake for 10 days	Reduce NO, MPO, MDA, IL-1 β , and IL-6 Increase activity of SOD and GSH-Px8	44
	Naringenin	4% acetic acid-induced UC rat	6 animals/group	Naringenin 25, 50, or 100 mg/kg per day	Oral intake for 1 week	Decrease INF- γ , PGE2, macrophage inflammatory protein (MIP-2), NO, IL-1 β , and IL-6	45,46
	Naringin	4% acetic acid-induced UC rat	6 animals/group	Naringin (40 and 80 mg/kg)	Oral intake for 1 week	Increase SOD and GSH Inhibit alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels	47
	APP	2.5% DSS-induced colitis mice	5 animals/group	1% APP	Oral intake for 2 weeks	Reduce IL-1 β , TNF- α , and IL-6	48
	Resveratrol	(1) 2.5% TNBS intracolonic instillation	(1) 10 animals/group	(1) Resveratrol (10 mg/kg)	(1) Oral intake for 2 weeks	(1) Decrease COX-1 and NF- κ B	49-51
		(2) 4 animals/group induced colitis rat	(2) 4 animals/group	(2) Resveratrol (10 mg/kg)	(2) Oral Intake for 1 week	(2) Downregulate iNOS, NF- κ B, STAT3, and ERK	
		(3) 25 patients/group DSS-induced colitis mice	(3) 25 patients/group	(3) Resveratrol (500 mg/person)	(3) Oral intake for 6 weeks	(3) Reduce expression levels of TNF α and NF- κ B	
	Curcumin	(3) Patients with UC	(1) 8 animals/group	(1) Curcumin 50 mg/kg	(1) Oral intake for 2 weeks	(1) Inhibit STAT3 activity	52,53
		(1) 5% DSS-induced colitis mice	(2) 7 animals/group	(2) Curcumin (100 mg/kg per day)	(2) Intraperitoneally injected for 1 week	Decrease TNF- α , and IL-1 β (2) Inhibit NLRP3 inflammasome. Decrease IL-1 β , IL-6, MCP-1, and MPO activity	

(continued)

TABLE 1. (CONTINUED)

Material	Main compound/ingredient	Species	Sample size	Effect size	Treatment	Mode of action	References
Fatty acids	Sophocarpine, sophoridine Berberine	5% DSS-induced colitis mice (1) 5% DSS-induced colitis rat (2) 2.5% TNBS-induced colitis mice	10 animals/group (1) 8 animals/group (2) 10 animals/group	Sophocarpine 60, 30, or 15 mg/kg (1) Berberine 10 or 50 mg/kg (2) Berberine 50 or 100 mg/kg	Oral intake for 1 week (1) Oral intake for 1 week (2) Oral intake for 5 or 9 days	Decrease IL-1 β , IL-6, colonic MPO activity (1) Decrease MPO, TNF- α , and IL-1 β and IL-6 Upregulate Nrf2 (2) Decrease IFN- γ , IL-17, IL-6, IL-1 β , and TNF- α Increase IL-22 level in the local colon	54–56 57,58
	Isatin	2.5% TNBS-induced colitis mice	8 animals/group	Isatin 6 or 10 mg/kg	Administered by means of an esophageal catheter for 3 days	Reduce colonic TNF- α , COX-2, and PGE2 levels Increase colonic IL-10	59
	Tryptanthrin (TRYP)	(1) 5% DSS-induced colitis mice (2) 5% DSS-induced colitis mice	(1) 6 animals/group (2) 6 animals/group	(1) TRYP 100 mg/kg (2) TRYP 39.2, 78.4, or 156.8 mg/kg	(1) Oral intake for 3–7 days (2) Oral intake for 2 weeks	(1) Decrease PGE2, TNF- α , and NO (2) Inhibit TNF- α /NF- κ B and IL-6/STAT3 pathway	60–62
	Caffeine	3.5% DSS-induced colitis mice	8 animals/group	Caffeine 2.5 mM	Oral intake for 18 days	Decrease chitinase 3-like 1-associated AKT activation	63
	Ginsenoside Rg1 Ginsenoside Rh1 Ginsenoside Rd	2.5% TNBS-induced colitis mice 3% DSS-induced colitis mice	6 animals/group 6 animals/group	Ginsenoside Rg1, Rh1 (20 mg/kg) Ginsenoside Rd 10, 20, 40 mg/kg	Oral intake for 3 days Oral intake for 10 days	Inhibit MPO activity, IL-1 β , IL-17, and TNF- α Inhibit NLRP3 inflammasome by p62-mediated mitophagy	64 65
	Ginsenoside Re	2.5% TNBS-induced colitis mice	10 animals/group	Ginsenoside Re 20 mg/kg	Oral intake for 3 days	Suppress NF- κ B	66
	Astragaloside IV	5% TNBS-induced colitis rat	16 animals/group	ASIV 10 mg/kg	Oral intake for 6 days	Stimulates nuclear translocation of β -catenin	67
	Long-chain n-3 PUFA	(1) IBD patients	(1) 230 IBD patients (168 UC, 62 CD)	Long-chain n-3 PUFA 2.76 g/day	Oral intake for 12–18 months	Reduce COX-2, IL-6, iNOS, and colon TNF- α	68–70
	n-3 PUFAs plus 5-ASA CLA	5% TNBS-induced colitis rat 4% DSS-induced colitis pig	13 animals/group 8 animals/group	n-3 PUFA +5-ASA 5–25 mg/kg CLA 2.21%	Oral intake for 2 weeks Oral intake for 42 days	Reduce NF- κ B activation Induce PPAR γ Enhance PPAR γ	71 72
	α -Eleostearic acid	2.5% DSS-induced colitis mice	5 animals/group	α -Eleostearic acid not determined	Oral intake for 7 days	Activate PPAR γ	73
	Alpha linoleic acid	5% DSS-induced colitis rat	8 animals/group	Alpha linoleic acid 5%	Oral intake for 7 days	Reduce IL-8, COX-2, and iNOS	74
	SCFA, butyrate	TNBS (100 mg/kg)-induced colitis rat	5–7 animals/group	Butyrate 0.5 mM/kg	Oral intake for 20 days	Decrease NF- κ B-induced TNF- α , IL-6, and iNOS	75–79

(continued)

TABLE 1. (CONTINUED)

<i>Material</i>	<i>Main compound/ingredient</i>	<i>Species</i>	<i>Sample size</i>	<i>Effect size</i>	<i>Treatment</i>	<i>Mode of action</i>	<i>References</i>
Bioactive peptides	Alanine-Glutamine	3% DSS-induced colitis mice	9 animals/group	Ala-Gln solution (0.5 g Gln/kg per day)	Intraperitoneally injected for 3 days	Reduce blood IL-17A and 17F	81
	Propionyl-L-carnitine +5-ASA	UC patients	23 patients	Propionyl-L-carnitine (1 g/day or 2 g/day) 5-ASA; (3.2 g/day)	Oral intake for 4 weeks	Decrease intestinal damage and microvascular dysfunction (reduces CD4 ⁺ lymphocytes, ICAM-1 ⁺ , and iNOS ⁺ microvessels)	82
	BGMP	2% DSS-induced colitis mice	8 animals/group	BGMP 15 mg/kg	Oral intake for 13 days	Increase IL-10	83,84
	Glucosamine oligomer	3% DSS-induced mice	8 animals/group	Glucosamine oligomer 2%	Oral intake for 5 days	Reduce MPO activity Inhibit NF- κ B and COX-2	85
	Collagen peptide derived from Alaska pollock skin	Human colonic adenocarcinoma Caco-2 cells (10 ng/mL TNF- α)	9 samples/group	Collagen peptide 2 mg/mL	Cell treatment for 48 h	Reduces TNF- α and IL-6 Suppress the NF- κ B and ERK1/2-mediated MLCK pathway	86
	Fish peptide derived from salmon	5% DSS-induced colitis rat	10 animals/group	Fish peptide 3–5%	Oral intake for 4 weeks	Downregulate inflammatory cytokine	87
	Oligophosphopeptides derived from hen egg yolk phosvitin	Human colonic adenocarcinoma Caco-2 cells (1 mM H ₂ O ₂)	3 samples/group	Oligophosphopeptides 0.5 mg/mL	Cell treatment for 2 h	Inhibit IL-8 secretion Enhance GSH levels	88,89
	Peptide derived from <i>Bubalus bubalis</i> milk-derived products (MBCP)	Human colonic adenocarcinoma Caco-2 cells (10 μ M TNF- α)	3 samples/group	MBCP (18 μ M)	Cell treatment for 48 h	Increase GST and CAT Inhibit NF- κ B pathway Reduce COX-2	90

5-ASA, 5-aminosalicylic acid; APP, Apple polyphenol; BGMP, bovine glycomacropeptide; CAT, catalase; CD, Crohn's disease; CLA, conjugated linoleic acid; COX-2, cyclooxygenase 2; DSS, dextran sodium sulfate; GSH, glutathione; GST, glutathione S-transferase; IBD, inflammatory bowel disease; IL, interleukin; INF, interferon; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; MPO, myeloperoxidase; NF- κ B, nuclear factor-kappa B; NO, nitric oxide; NLRP3, NOD-like receptor pyrin domain-containing 3; PGE2, prostaglandin E2; PPAR γ , peroxisome proliferator-activated receptor- γ ; PUFA, polyunsaturated fatty acid; SCFA, short-chain fatty acid; SOD, superoxide dismutase; TNBS, 2, 4, 6-trinitrobenzene sulfonic acid; TNF- α , tumor necrosis factor alpha; UC, ulcerative colitis.

Fatty acids

Polyunsaturated fatty acids (PUFAs) reportedly modulate the immune response and contribute to ameliorating the symptoms of inflammatory diseases. The therapeutic effect of PUFAs on IBD has long been demonstrated, and the results suggest that dietary PUFA intake is to be a good strategy for preventing or improving IBD.⁶⁸ A recent study has reported that a high dietary long-chain n-3 PUFAs intake reduces the risk of UC.⁶⁹ N-3 PUFA was shown to protect against intestinal inflammation in a rodent TNBS-induced colitis models. In addition, a recent study has demonstrated that n-3 PUFA significantly reduced COX-2, IL-6, colon iNOS, and colon TNF- α production compared with the control diet, indicating that dietary n-3 PUFA can ameliorate colitis development by downregulating inflammatory markers.⁷⁰ A previous study demonstrated that dual therapy of n-3 PUFAs plus 5-aminosalicylic acid (5-ASA) is more effective than only 5-ASA at reducing NF- κ B activation and inducing peroxisome proliferator-activated receptor- γ (PPAR γ) in a colitis model.⁷¹

A previous study concluded that conjugated linoleic acid (CLA) supplementation enhanced PPAR γ expression in the colon and contributed to retarding the onset of IBD. CLA was tested in a clinical study of patients with CD.⁷² Dietary α -eleostearic acid, which has been found in bitter melon seed oils, improved the symptoms of IBD model mice by activating PPAR γ .⁷³ Alpha linoleic acid supplementation was shown to effectively inhibit IL-1 β -induced inflammation by downregulating mRNA levels of proinflammatory genes such as IL-8, COX-2, and iNOS.⁷⁴

The number of bacteria-producing short-chain fatty acids (SCFA) was decreased in the mucous membranes and feces of patients with IBD. SCFAs, which mainly include acetate (C2), propionate (C3), and butyrate (C4), are necessary metabolites in the regulation of intestine homeostasis. Some studies have demonstrated that the levels of SCFA are significantly decreased in patients with IBD. SCFA plays a key role in the IECs and contributes to strengthening the intestinal barrier.⁷⁵ Butyrate possesses beneficial effects for IECs and immune cells by increasing the levels of anti-inflammatory mediators (e.g., IL-10) but decreasing the expression of NF- κ B-induced TNF- α , IL-6, and iNOS. Butyrate also strengthens the epithelial barrier function by inducing tight junction components and contributes to protein reassembly by activating transcription factors such as STAT3 and SP1.^{76–79}

Bioactive peptides

Dietary peptides derived from food possess bioactive properties that are healthful for preventing disease.⁸⁰ Some bioactive peptides show potential for use as alternative IBD treatments. Post-treatment with alanine-glutamine inhibited the expression of Th17-associated cytokines, decreased the peritoneal cavity of macrophage infiltration, and reduced the secretion of proinflammatory cytokine in DSS-induced colitis.⁸¹

The oral and intrarectal administration of propionyl-L-carnitine, an ester of L-carnitine necessary for the mito-

chondrial transport of fatty acids, significantly decreased intestinal impairment and microvascular dysfunction in rat TNBS-induced colitis.⁸² Bovine glycomacropeptide (BGMP), a 64-amino-acid peptide derived from the digestion of milk k-casein, showed immunomodulatory, antimicrobial, and possibly prebiotic activities. BGMP significantly reduced mucosal impairment in the colon and contributed to increasing IL-10 expression in lymphocyte-driven colitis.⁸³ In addition, the oral administration of BGMP showed anti-inflammatory effects in an experimental colitis model.⁸⁴

Orally administered glucosamine oligomer exhibited anti-inflammatory effects by suppressing the activation of both NF- κ B and COX-2 in a DSS-induced colitis model.⁸⁵ Collagen peptide derived from Alaska pollock skin ameliorated TNF- α -induced barrier dysfunction in Caco-2 cells by suppressing the NF- κ B and ERK1/2-mediated MLCK pathways.⁸⁶ Fish peptide derived from salmon by enzymatic hydrolysis showed fewer signs of histopathological inflammation and downregulation of inflammatory cytokines in a DSS-induced colitis.⁸⁷ Oligophosphopeptides derived from hen egg yolk inhibited the secretion of IL-8 in H₂O₂-induced Caco-2 cells but enhanced the levels of GSH and increased catalase, glutathione S-transferase, and γ -glutamyl-cysteine synthetase activities.^{88,89} A peptide derived from *Bubalus bubalis* milk-derived products strengthened the organization of adherent epithelial junctions, inhibited the NF- κ B pathway, and decreased intestinal permeability.⁹⁰

CONCLUSIONS

Although candidate disease-related targets of IBD are being found, the key factors have not been identified. Therefore, many kinds of research regarding the complex interaction among these disease-related targets should be continuously performed.

Long-term treatment of current drugs for curing IBD can cause side effects such as bone alterations or osteoporosis in the case of using glucocorticoids, and nutritional therapy may be an alternative intervention to improve IBD symptoms. In addition, the fact that IBD is predominant in westernized countries and that the number of patients is increasing in Asia, where recent western food is increasing, suggests that dietary modifications may be important for the treatment of IBD. As previously described, many functional foods and nutraceuticals are effective for inflammation and damaged barrier permeability, which are representative symptoms of IBD. In the future, human studies and clinical trials evaluating the best combinations of multiple functional foods and nutraceuticals, which possess anti-inflammatory and/or immunomodulatory properties, will be important for improving IBD therapy.

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AUTHOR DISCLOSURE STATEMENT

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