OPEN ACCESS J PREV MED HYG 2022; 63(SUPPL. 3): E214-E220

REVIEW

Dietary supplements for intestinal inflammation

AYSHA KARIM KIANI[1], GABRIELE BONETTI[2,*], KEVIN DONATO[1], MATTEO BERTELLI[1,2,3]
[1] MAGI Euregio, Bolzano, Italy; [2] MAGI'S LAB, Rovereto (TN), Italy; [3] MAGISNAT, Peachtree Corners (GA), USA

Keywords

Mediterranean diet • Intestinal inflammation • Dietary supplements • Inflammatory bowel disease • Dysbiosis

Summary

Intestinal inflammation leads to various chronic diseases, collectively known as inflammatory bowel disease (IBD). IBD mainly affects the large intestine, but it can also affect the gastrointestinal tract as a whole. Its major symptoms are pain, diarrhea, and weight loss, and it is usually associated with deficiencies of both macro- and micronutrients. Unluckily, after some time the body develops resistance against the already available drugs: thus, many patients fail to maintain remission, which is achieved in less than 50% of cases. Diet is a major determinant of gut inflammation. An unbalanced diet can affect the gut microbiota and cause dysbiosis, which is related to a dysregulated host immune response. The Mediterranean Diet its renowned for its anti-inflammatory effects and for preventing dysbiosis. In order to improve management and treatment of intestinal inflammatory diseases, it should become common practice to integrate the patient's diet with dietary supplements with anti-inflammatory effects (probiotics, butyrate, phosphatidylcholine, lactoferrin, palmitoylethanolamide, silymarin, and omega 3), which maintain the stability of the intestinal microbial cohort and strengthen the mucosal barrier, thus preventing or soothing IBD symptoms. Dietary supplements may help fight the high costs, the adverse side effects, and the recurrent relapses typical of drug use.

Introduction

Inflammation is an innate immunity mechanism, triggered by the complex biological response of the gut as well as of other tissues of the body toward harmful stimuli, like pathogenic bacteria [1]. The inflammatory bowel disease (IBD) consists of two heterogeneous chronic immune disorders, namely Crohn's disease (CD), affecting the whole gastrointestinal tract, and ulcerative colitis (UC), mainly affecting the large intestine [2]. With the advancement of technology and better understanding of the gastrointestinal pathophysiology, mucosal immunology and microbiology, research studies are now focused on the effects of diet on IBD pathogenesis [3]. To some extent, the increasing IBD incidence has been linked to the highly processed diet (Western diet), characterized by higher concentrations of fats and refined sugars. IBD patients present deficiencies both in macronutrients and in certain micronutrients. The major symptoms of IBD include abdominal pain, diarrhea, and sometimes weight loss [2].

Regardless of the availability of many novel drugs for IBD treatment, clinical remission is still achieved in less than 50% of patients, and even the initially responsive IBD patients eventually developed non-responsiveness, leading to further progression of disease as well as worsened quality of life. According to researchers, the role of diet in the clinical management of IBD patients is underestimated. Diet is considered as one of the major determining factor of gut microbiota, and an imbalanced diet could lead to dysbiosis and to many other effects on host homeostasis [4]. Gut dysbiosis is a major contributor to host immune response in various IMIDs (immune-mediated inflammatory diseases) [5]. Moreover, dysbiosis is known to directly or indirectly induce and sustain intestinal inflammation and to promote adipose tissue development. A diet with higher fat content increases intestinal permeability, thus leading to an excessive bacterial influx, which in turn causes the lack of tolerance for microbiota-derived antigens as well as gut inflammation among IBD patients [4].

The Mediterranean diet, comprised of olive oil, vegetables, fruits, whole grains, yogurt, and red wine, is famously associated with inflammation reduction and showed positive effects in IBD patients [4]. Particularly, extra-virgin olive oil (EVOO) is renowned for its nutritional characteristics as well as health benefits, specifically against inflammation and gastrointestinal (GI) tract diseases [6]. Experimental evidence suggested that the Mediterranean diet could have a preventive role in the onset of dysbiosis by favoring the existence of bacterial species with specific anti-inflammatory properties [4].

Lately, the use of various supplementations containing probiotics, butyrate, phosphatidylcholine, lactoferrin, palmitoylethanolamide (PEA), silymarin, and omega 3 has been strongly suggested to patients suffering from inflammatory diseases [2]. There are strong rationales to suspect the significant therapeutic potential of these dietary supplements in inflammatory bowel disease, which is a chronic intestinal disease with no medical cure [5]. The high price, the adverse side effects, and the recurrent relapses linked with the drugs usually prescribed have endorsed the need for alternative treatment options for many IBD patients [2]. We will now discuss each of the above-mentioned supplements in detail.

https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2763

Probiotics

Probiotics are live microorganisms that are added to fermented foods and are beneficial for health because they improve the overall stability of the intestinal microbial cohort. Probiotics possess immunomodulating properties that influence the intestinal microbial cohort and reduce the activity of intestinal pathobionts, like *Clostridium perfringens* and *Klebsiella pneumonia* [7].

Particular commensal species, known as novel probiotics or next-generation probiotics, restore intestinal health by inhibiting inflammation and restoring the epithelial barrier. These goals could be achieved either by *de novo* administration of specific microbial species to the gut as probiotic/bacterio-therapeutic preparations or by growth acceleration of particular species within the gut through dietary means, or by combining these methods. The main intestinal phyla are the Lactobacilli – that cause a significant reduction in the number of toxin-producing intestinal bacteria as well as increase in longevity – and Bifidobacteria – that protect the intestinal health thanks to the substances they secrete or their extracellular structures. *Eubacterium hallii*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis* metabolize the dietary fibers and provide energy for enterocytes, also providing anti-inflammatory effects within the gut. *Akkermansia muciniphila* exerts a beneficial effect on metabolic syndrome and strengthens the gut mucosal barrier. Recently, Bacteroides species have been reported to release immunomodulatory molecules with further beneficial effects [8].

Clinical studies provide evidence supporting the beneficial effects of probiotics in the prevention as well as in the treatment of numerous gastrointestinal diseases in both adult and pediatric patients. Therefore, evidence-based probiotic formulations could be given to prevent or decrease the intensity of intestinal inflammations modulated by pathogenic bacteria. Probiotic supplementation could also be used to treat inflammation-associated complications of inflammatory bowel diseases. *In vivo* studies have also reported the effectiveness of probiotics in the prevention or reduction of inflammatory responses linked with colitis [7, 8].

The probable mechanisms of action of probiotic supplementation have been studied under various experimental conditions, both *in vivo* and *in vitro*. The efficacy of probiotics depends upon several factors, including the agents used, total dose and dosing pattern, their metabolism, the metabolites they produce, the molecules expressed on their surface, the characteristics of the host and luminal microbial environment. [8]

In a recent research study Kim et al. supported probiotic supplementation in inflammatory bowel disease by exhibiting that LA1 (*Lactobacillus acidophilus*) significantly affects endoplasmic reticulum stress and suppresses the activation of NF-$\varkappa$B (which leads to IBD pathogenesis), and could therefore be used as a potential immunomodulator in IBD treatment [9].

Probiotics are also employed to treat celiac disease, a prevalent systemic disorder affecting the small intestine and caused by an abnormal immunity response to the ingestion of gluten: since probiotics can regulate the composition as well as the functions of the microbiota, their supplementation might delay or even prevent the disease onset. Probiotics modulate immune response, toxin receptors degradation, nutrients competition, adhesion sites blockage, and the production of inhibitory substances against pathogens [10, 11]. Lindfors et al. [12] have highlighted that certain probiotics, like *Bifidobacterium lactis* or *Lactobacillus fermentum*, play a protective role against gliadin toxic effects in cultures of intestinal cells (Caco-2 cells from the human colon), causing a dose-dependent inhibition of the amplified intestinal epithelial permeability induced by the stimulation of gliadin and the production of IL-10 by T- regulatory cells [11, 12].

Certainly, the major symptoms of the condition are caused by the inflammation activation via cytokines cascade induction through the NF-κB pathway. Other strains of Bifidobacteria improve the composition of gut bacteria in celiac disease and reduce the inflammation, as evidently reported by Laparra et al. [13]. Another research study by Laparra et al. shows that Bifidobacteria and gliadin-digested fragments cause the downregulation of the mRNA expression of proinflammatory cytokines, like NF-kB, IL-1beta and TNF-a [14]. Besides, *Lactobacillus casei* has shown beneficial effects in the celiac disease for GALT (gut-associated lymphoid tissue) recovery and homeostasis, restoring a healthy mucosal structure [15]. These unconventional and promising probiotics could further contribute to biotherapeutic strategies in the future [11, 15].

Butyrate

Butyric acid is a fatty acid, produced by colonic bacteria from the fermentation of dietary fiber [1]. Butyrate plays a significant role in intestinal health because of its anti-inflammatory and regenerative properties. Other than regulating the colon motility, blood flow, and pH, butyric acid also improves the mucosal function as well as the epithelial barrier of the intestine. Besides, it possesses anti-inflammatory, antioxidant, antimicrobial and antineoplastic properties and offers a significant energy source for the colonocytes [16].

Decreased butyrate oxidation is observed in the biopsy of large bowel mucosal specimens of quiescent ulcerative colitis (UC) patients. Recently, research studies have demonstrated that Sodium Butyrate (NaB) displays anti-inflammatory properties by inhibiting the production of interleukin (IL)-12, caused by the suppression of both IL-12p40 and IL-12p35 mRNA accumulation, and also enhances the release of IL-10 in *S. aureus*-induced human monocytes [17]. The lack of NaB in diets poor in carbohydrates could cause clinically relevant functional alterations [16, 18].

Butyrate and short-chain fatty acids (SCFA) are likely candidates for novel therapeutic approaches. Butyrate plays a vital role in mucosal repair by non-transgluta-

minase-mediated as well as transglutaminase-mediated pathways, dilatation of arterioles, increase in oxygen uptake and mucosal blood flow, reduction of mucosal permeability as well as increase in mucosal production and its release. The effectiveness of sodium butyrate in enhancing repair of the mucosal lesions and in decreasing associated symptoms further strengthens its role in treating and managing UC as well as other mucosal disorders of the colon [19].

The amount of BCoAT (butyryl-CoA acetate CoA-transferase) has been found to be significantly decreased in Crohn's disease (CD) patients, suggesting a genetic inability of the microbes to synthesize butyrate in CD subjects. Therefore, many interventional studies as well as randomized clinical trials have analyzed and established butyrate effectiveness in reducing various disease symptoms, especially underlying inflammation. Previously, UC patients were given butyrate as enemas, while CD patients were given butyrate as oral tablets, with reduced intestinal surface diffusion capacity. Recently, researchers have highlighted that the absence of butyrate might change gut homeostasis by increasing lumen oxygen concentration, thus decreasing the concentration of butyrate-producing bacteria [20-22].

Recently, a novel oral formulation of butyrate (ButyroseR Lsc Microcaps-BLM) has been prepared where butyrate is enclosed in a lipophilic microcapsule, thus providing enhanced intestinal diffusion and facilitating the gradual release of the active ingredient [23]. This type of oral formulation allows butyrate absorption even in distal parts of the colon.

Previously, microencapsulated sodium butyrate (MSB) has been linked with regenerative and anti-inflammatory properties of the large bowel mucosa. MSB provides symptomatic relief from various colonic diseases, like IBD, malabsorption and diarrhea. Sodium butyrate (NaB) regulates intestinal environment, modulates intestinal permeability, decreases oxidative stress, and restores the colonic defense barrier, reducing mucosal inflammation and enhancing cell regeneration, as well as promoting tissue healing, without significant side effects [24, 25].

A randomized, double-blinded, placebo-controlled pilot study by Facchin et al. [20] analyzed the effectiveness of the oral formulation of microencapsulated sodium butyrate on gut microbiota in IBD patients. Butyrate administration enhances bacterial growth, which in turn leads to higher butyrate production. Exogenous butyrate could regulate gut bacteria and stimulate the growth of butyrogenic as well as SCFA genera, which in turn produce additional endogenous butyrate for intestinal homeostasis restoration.

Emmi et al. [26], in their proof-of-concept trial, showed for the first time that butyrate-enriched diets can regulate the blood redox status and stimulate fibrin degradation, which is diminished by a neutrophil-dependent mechanism (via ROS) among Behçet's syndrome patients. Similarly, butyrate-enriched supplementation resulted in a major reduction of blood inflammatory parameters, such as leukocyte ROS production and peroxidation of plasma lipids. Particularly, a significant improvement was observed in the susceptibility of fibrin for plasmin-induced lysis [26].

Many clinical studies have reported the decrease of visceral pain in IBD patients treated with NaB. The anti-inflammatory as well as the trophic effect of NaB could be beneficial for the patients suffering from IBD, diverticulitis, diarrhea, malabsorption, and cachexia. NaB is an essential component of gut hemostasis and it is crucial for natural regeneration within the intestinal epithelium. Several pathological processes affecting the large intestine may be linked with reduced endogenous levels of butyric acid. Several studies showed that the reduction in the frequency of irritable bowel syndrome (IBS) symptoms by the administration of microencapsulated sodium butyrate (MSB) might be caused by the reduction of intestinal receptors oversensitivity, leading to lower intraintestinal pressure amplitude [27]. The absence of side effects shows that MSB treatment is well tolerated and safe as a supplemental treatment for standard IBS therapy [25, 27, 28].

Phosphatidylcholine

Any disturbance in the mucosal barrier acts as an initiating factor that leads to attacks from commensal colonic bacterial flora, causing mucosal inflammation. Phospholipids, among the main components of the mucosa, consists of almost 90% phosphatidylcholine (PC) as well as lysophosphatidylcholine (LPC). Phosphatidylcholine plays a major role in the mucosal defense by creating a protective hydrophobic layer; whereas a defective phosphatidylcholine layer might lead to inflammation or even ulceration [29]. Additionally, phosphatidylcholine along with other lipids inhibits proinflammatory signaling in macrophages-derived phagosome model systems. On the other hand, the intrinsic mucus phosphatidylcholine content in UC was significantly reduced, regardless of the degree of mucosal inflammation [30]. Moreover, a local increase in the concentration of phosphatidylcholine in colonic mucus might improve the functions of the intestinal barrier, reducing inflammation in UC patients [29]. Thus, phosphatidylcholine supplementation might be helpful in order to restore the structure as well as the density necessary for the mucus to act as a protective mechanical barrier. Moreover, phosphatidylcholine could also be integrated in the mucosal cell membrane, where it affects the signaling processes associated with inflammation. The latest *in vitro* studies, involving a phagosomal analysis model system, validate the involvement of phosphatidylcholine in the signaling networks linked to the inhibition of proinflammatory signaling [29, 31, 32]. Phosphatidylcholine supplementation is considered as one of the most promising therapeutic strategies for colonic mucus. Stremmel et al. [33] showed that in 80% of the steroid-refractory UC patients, phosphatidylcholine successfully replaced steroid treatment. Almost half of the patients supplemented with phosphatidylcholine had shown more than 50% improvement in their clinical

activity index, which is linked with histologic and endoscopic activities and ultimately improves the quality of life. Phosphatidylcholine exhibits an enhanced safety profile and seems to be effective in shorter time as compared to 6-mercaptopurine or azathioprine [33].
The oral ingestion of phosphatidylcholine is completely absorbed in the upper intestinal tract, while the topical rectal administration of phosphatidylcholine fails to integrate in the mucus. This is why the best way for administering phosphatidylcholine was to encapsulate it with Eudragit-S100 (Rohm Pharma, Darmstadt, Germany), to offer pH-dependent release within the distal region of the intestinal tract [33, 34].
The basic idea behind this retarded release phosphatidylcholine (rPC) preparation was that the absence of phosphatidylcholine in the colonic mucus induces inflammation within ulcerative colitis. Two earlier studies have provided evidence of the therapeutic effectiveness of rPC in controlling inflammation in chronic UC patients with active non-steroid treatment, as well as steroid refractory UC. The results of the first study revealed 70% improvement in disease activity among chronic-active UC patients with a non-steroid treatment. The results of the second study showed clinical remission among 50% of the chronic steroid-refractory UC patients, and they could eventually discontinue the steroid therapy [30, 33, 34]. Some animal studies have also reported that when phosphatidylcholine is topically applied on the colon region, it protects those animal models against trinitrobenzenesulphonic or acetic acid-induced colitis [29].
In a prospective, double blind, randomized, placebo-controlled study Stremmel et al. [33], evaluated the clinical effectiveness of retarded release of an oral phosphatidylcholine preparation among 60 patients having chronic, non-steroid dependent and active UC. Their results strongly suggest that phosphatidylcholine supplementation has a significant therapeutic potential against UC [29]. Long-term supplementation of phosphatidylcholine might be helpful in maintaining the clinical remission without the adverse effects that are usually observed after immunosuppressive and steroid therapies [29].

Lactoferrin

Lactoferrin is a multifunctional iron-binding glycoprotein that is found in significant concentrations in different human mucosal secretions, especially breast milk. Lactoferrin accounts for almost 25% of the breast milk protein content (1-3 g/mL), it chelates iron and inhibits bacterial growth. The antimicrobial properties of lactoferrin have been established *in vitro* as well as *in vivo*, proving its potential benefits on intestinal health. Lactoferrin improves the hematocrit levels and reduces the rate of lower respiratory tract and gut infections in infants, without adverse effects [35].
A research study focusing on the administration of transgenic milk supplementation comprised of human lactoferrin to malnourished pigs resulted in decreased intestinal permeability and beneficial effects on the jejunal structure, along with significant weight gain [36]. Lactoferrin, in combination with lysozyme, acts as a bactericidal agent for both Gram-positive and Gram-negative bacteria; in fact, lactoferrin, thanks to its ability to chelate iron and to bind with membrane lipopolysaccharides, disrupts the outer membrane, whereas lysozyme acts upon the inner peptidoglycan cell wall. Notably, both lactoferrin as well as lipopolysaccharides show resistance against proteolytic degradation, which is an essential requirement for the therapeutic use of any oral agent in humans [37].
In a Peruvian study on children, ranging from 5 to 33 months of age, oral supplementation of lactoferrin containing rehydration solutions decreased the duration and severity of diarrheal episodes in patients with acute diarrhea and dehydration, with no adverse effects [38]. Because of these therapeutic properties, lactoferrin is considered as an attractive candidate for preventing as well as treating environmental enteric dysfunction (a chronic subclinical inflammatory condition of the gut). Generally, lactoferrin is considered a beneficial supplement for the neonates who could not have breast milk or those who are weaning but might still take advantage from its therapeutic properties [35].

Palmitoylethanolamide (PEA)

The activation of the intestinal immune system as well as an imbalance in the endocannabinoid system are involved in IBS pathophysiology, which is why the supplementation of endocannabinoid-like nutritional compounds might improve IBS symptoms, specifically abdominal pain. Particularly, palmitoylethanolamide (PEA) is an endogenous fatty acid amide, most abundant in peanuts and egg yolk, which has been repeatedly reported to perform anti-inflammatory as well as analgesic activities both *in vivo* and *in vitro* [39, 40].
The palmitoylethanolamide treatment was reported to be noticeably effective in decreasing abdominal pain severity in IBS. Palmitoylethanolamide and polydatin are nutritional compounds that act synergistically to decrease the activation of mast cells [39].
Palmitoylethanolamide has lower affinity for the cannabinoid receptors and regulates inflammation as well as nociception, which mainly occurs by the down-regulation of mast cell activity. Interestingly, the Nobel laureate Rita Levi-Montalcini recognized that palmitoylethanolamide might act as a mast cell modulator, as well as a potential agonist of PPAR-a (Peroxisome proliferator-activated receptor-alpha), CB2 (cannabinoid type 2) receptors, TRPV1 (transient receptor potential vanilloid type 1), and orphan GPCR (G protein coupled receptor). In addition, several research studies have statistically established that the palmitoylethanolamide-polydatin treatment was effective on abdominal pain severity, if not on its frequency [40, 41].

Silymarin

Silymarin, an extract from *Silybum marianum* seeds, is a natural source of flavanolignans complex that exhibits strong intracellular antioxidant properties. In addition to hepatoprotective effects, silymarin also possess beneficial effects on the regulation of immune-mediated murine colitis through bowel histology restoration and on the decrease of certain bowel inflammatory cytokines – specifically, NF-$\varkappa$B (nuclear factor $\varkappa$B), TNF-α, and IL-1β (interleukin-1β). Additionally, there is a correlation between NF-$\varkappa$B inhibition and colitis activity reduction in rat models after treatment with silibinin (the major silymarin flavanolignan component) and ursodeoxycholic acid [42, 43].

Recent research studies have reported that the use of Silymarin on UC patients has many beneficial effects: treated patients were reported to remain in a remission state and to tolerate the drug well. These beneficial effects are probably due to its anti-oxidative properties. The data from several clinical studies as well as animal studies have also reported beneficial effects of Silymarin on hemoglobin concentration (Hb), TNF-α, IL-1β, lipid peroxidation, erythrocyte sedimentation rate (ESR), bowel cell myeloperoxidase, and cell histology. These clinical trial results thus support the hypothesis that silymarin supplementation is useful to maintain remission in UC patients [44].

Omega 3

The significant and beneficial role of dietary omega-3 in inflammation is well established. There is epidemiological evidence of reduced incidence of inflammatory and autoimmune disorders in those who take these polyunsaturated fatty acids (PUFAs). Since TNF and IL-1 are the main inflammation mediators, a decrease in the production of these cytokines contributes to the improvement of inflammatory symptoms among patients treated with omega-3 supplements; however, the exact step of the inflammation pathway at which these therapeutic agents have their maximum effect is still to be defined [45].

A double–blind, placebo-controlled crossover study by Stenson et al. [46], involving fish oil supplementation as well as a placebo group, showed that fish oil supplementation increases B5 production, reduces B4 production and also decreases the contents of leukotrienes rectal dialysates. Also Belluzzi et al. [47] reported a decreased rate of relapse among Crohn's disease patients that are in remission after the supplementation of 2.7 grams of omega-3 enteric-coated fish oil preparation. Similarly, Endres et al. [48] have evaluated the therapeutic effect of omega-3 fatty acid in IBD patients and reported that many studies have mentioned a significant improvement in the clinical activity as well as steroid-sparing effects. However, other studies only showed a trend towards improvement, without reaching significance [45, 48].

Conclusion

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), is characterized by chronic intestinal inflammation and is influenced by the composition of the gut microbiota. IBD greatly affects the patients' quality of life and most of the currently used drugs show non-responsiveness after some time, failing to achieve remission in more than 50% of patients. As diet is a major factor in the maintenance of gut microbiota, several components of the Mediterranean diet, especially extra-virgin olive oil (EVOO), are being studied and show anti-inflammatory properties and benefits for intestinal health. Recently, the use of various supplementations containing probiotics, butyrate, phosphatidylcholine, lactoferrin, palmitoylethanolamide (PEA), silymarin and omega-3 has been proposed to treat patients with inflammatory gut diseases. Since these supplements are known to exert anti-inflammatory effects within the gut, to improve the stability of the intestinal microbial cohort, to strengthen the barrier function of the mucosa and to have no side effects, they should be considered for the treatment and management of intestinal inflammation.

Acknowledgements

This research was funded by the Provincia Autonoma di Bolzano in the framework of LP 15/2020 (dgp 3174/2021).

Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; AKK, GB, KD: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

References

[1] Lauridsen C. From oxidative stress to inflammation: redox balance and immune system. Poult Sci 2019;98:4240-6. https://doi.org/10.3382/ps/pey407

[2] Rossi RE, Whyand T, Murray CD, Hamilton MI, Conte D, Caplin ME. The role of dietary supplements in inflammatory bowel disease: a systematic review. Eur J Gastroenterol Hepatol 2016;28:1357-64. https://doi.org/10.1097/MEG.0000000000000728

[3] Ghishan FK, Kiela PR. Vitamins and minerals in inflammatory bowel disease. Gastroenterol Clin North Am 2017;46:797-808. https://doi.org/10.1016/j.gtc.2017.08.011

[4] Chicco F, Magrì S, Cingolani A, Paduano D, Pesenti M, Zara F, Tumbarello F, Urru E, Melis A, Casula L, Fantini MC, Usai P. Multidimensional Impact of Mediterranean Diet on IBD Patients. Inflamm Bowel Dis 2021;27:1-9. https://doi.org/10.1093/ibd/izaa097

[5] Jadhav P, Jiang Y, Jarr K, Layton C, Ashouri JF, Sinha SR. Efficacy of Dietary Supplements in Inflammatory Bowel Disease and Related Autoimmune Diseases. Nutrients 2020;12:2156. https://doi.org/10.3390/nu12072156

[6] Romani A, Ieri F, Urciuoli S, Noce A, Marrone G, Nediani C, Bernini R. Health Effects of Phenolic Compounds Found in Extra-Virgin Olive Oil, By-Products, and Leaf of Olea europaea L. Nutrients 2019;11:1776. https://doi.org/10.3390/nu11081776

[7] Vitetta L, Vitetta G, HallS. Immunological tolerance and function: associations between intestinal bacteria, probiotics, prebiotics, and phages. Front Immunol 2018:2240. https://doi.org/10.3389/fimmu.2018.02240

[8] Abraham BP, Quigley EM. Probiotics in inflammatory bowel disease. Gastroenterol Clin North Am 2017;46:769-82. https://doi.org/10.1016/j.gtc.2017.08.003

[9] Kim DH, Kim S, Lee JH, Kim JH, Che X, Ma HW, Seo DH, Kim TI, Kim WH, Kim SW, Cheon JH. Lactobacillus acidophilus suppresses intestinal inflammation by inhibiting endoplasmic reticulum stress. J Gastroenterol Hepatol 2019;34:178-85. https://doi.org/10.1111/jgh.14362

[10] Vanderpool C, Yan F, Polk BD. Mechanisms of probiotic action: implications for therapeutic applications in inflammatory bowel diseases. Inflamm Bowel Dis 2008;14:1585-96. https://doi.org/10.1002/ibd.20525

[11] Marasco G, Cirota GG, Rossini B, Lungaro L, Di Biase AR, Colecchia A, Volta U, De Giorgio R, Festi D, Caio G. Probiotics, Prebiotics and Other Dietary Supplements for Gut Microbiota Modulation in Celiac Disease Patients. Nutrients 2020;12:2674. https://doi.org/10.3390/nu12092674

[12] Lindfors K, Blomqvist T, Juuti-Uusitalo K, Stenman S, Venäläinen J, Mäki M, Kaukinen K. Live probiotic Bifidobacterium lactis bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. Clin Exp Immunol 2008;152:552-8. https://doi.org/10.1111/j.1365-2249.2008.03635.x

[13] Laparra JM, Sanz Y. Bifidobacteria inhibit the inflammatory response induced by gliadins in intestinal epithelial cells via modifications of toxic peptide generation during digestion. J Cell Biochem 2010;109:801-7. https://doi.org/10.1002/jcb.22459

[14] Laparra JM, Olivares M, Gallina O, Sanz Y. Bifidobacterium longum CECT 7347 modulates immune responses in a gliadin-induced enteropathy animal model. PloS One 2012;7:e30744. https://doi.org/10.1371/journal.pone.0030744

[15] D'Arienzo R, Stefanile R, Maurano F, Mazzarella G, Ricca E, Troncone R, Auricchio S, Rossi M. Immunomodulatory effects of Lactobacillus casei administration in a mouse model of gliadin-sensitive enteropathy. Scand J Immunol 2011;74:335-41. https://doi.org/10.1111/j.1365-3083.2011.02582.x

[16] Roda A, Simoni P, Magliulo M, Nanni P, Baraldini M, Roda G, Roda E. A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon. World J Gastroenterol 2007;13:1079-84. https://doi.org/10.3748/wjg.v13.i7.1079

[17] Säemann MD, Böhmig GA, Osterreicher CH, Burtscher H, Parolini O, Diakos C, Stöckl J, Hörl WH, Zlabinger GJ. Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. FASEB J 2000;14:2380-2. https://doi.org/10.1096/fj.00-0359fje

[18] Coradini D, Pellizzaro C, Marimpietri D, Abolafio G, Daidone MG. Sodium butyrate modulates cell cycle-related proteins in HT29 human colonic adenocarcinoma cells. Cell Prolif 2000;33:139-46. https://doi.org/10.1046/j.1365-2184.2000.00173.x

[19] Vernia P, Fracasso PL, Casale V, Villotti G, Marcheggiano A, Stigliano V, Pinnaro P, Bagnardi V, Caprilli R. Topical butyrate for acute radiation proctitis: randomised, crossover trial. Lancet 2000;356:1232-5. https://doi.org/10.1016/s0140-6736(00)02787-2

[20] Facchin S, Vitulo N, Calgaro M, Buda A, Romualdi C, Pohl D, Perini B, Lorenzon G, Marinelli C, D'Incà R, Sturniolo GC, Savarino EV. Microbiota changes induced by microencapsulated sodium butyrate in patients with inflammatory bowel disease. Neurogastroenterol Motil 2020;32:e13914. https://doi.org/10.1111/nmo.13914

[21] Di Sabatino A, Morera R, Ciccocioppo R, Cazzola P, Gotti S, Tinozzi FP, Tinozzi S, Corazza GR. Oral butyrate for mildly to moderately active Crohn's disease. Aliment Pharmacol Ther 2005;22:789-94. https://doi.org/10.1111/j.1365-2036.2005.02639.x

[22] Scheppach W, Sommer H, Kirchner T, Paganelli GM, Bartram P, Christl S, Richter F, Dusel G, Kasper H. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology 1992;103:51-6. https://doi.org/10.1016/0016-5085(92)91094-k

[23] Lorenzon M. Process for the production of an n-butyric acid compound in micro encapsulated form, for animal or human consumption. Google Patents 2013

[24] Krokowicz L, Stojcev Z, Kaczmarek BF, Kociemba W, Kaczmarek E, Walkowiak J, Krokowicz P, Drews M, Banasiewicz T. Microencapsulated sodium butyrate administered to patients with diverticulosis decreases incidence of diverticulitis--a prospective randomized study. Int J Colorectal Dis 2014;29:387-93. https://doi.org/10.1007/s00384-013-1807-5

[25] Banasiewicz T, Krokowicz Ł, Stojcev Z, Kaczmarek BF, Kaczmarek E, Maik J, Marciniak R, Krokowicz P, Walkowiak J, Drews M. Microencapsulated sodium butyrate reduces the frequency of abdominal pain in patients with irritable bowel syndrome. Colorectal Dis 2013;15:204-9. https://doi.org/10.1111/j.1463-1318.2012.03152.x

[26] Emmi G, Bettiol A, Niccolai E, Ramazzotti M, Amedei A, Pagliai G, Taddei N, Sofi F, Fiorillo C, Prisco D, Becatti M. Butyrate-rich diets improve redox status and fibrin lysis in Behçet's Syndrome. Circ Res 2021;128:278-80. https://doi.org/10.1161/CIRCRESAHA.120.317789

[27] Garland EL, Gaylord SA, Palsson O, Faurot K, Douglas Mann J, Whitehead WE. Therapeutic mechanisms of a mindfulness-based treatment for IBS: effects on visceral sensitivity, catastrophizing, and affective processing of pain sensations. J Behav Med 2012;35:591-602. https://doi.org/10.1007/s10865-011-9391-z

[28] Bengtsson M, Hammar O, Mandl T, Ohlsson B. Evaluation of gastrointestinal symptoms in different patient groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterol 2011;11:122. https://doi.org/10.1186/1471-230X-11-122

[29] Stremmel W, Merle U, Zahn A, Autschbach F, Hinz U, Ehehalt R. Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. Gut 2005;54:966-71. https://doi.org/10.1136/gut.2004.052316

[30] Stremmel W, Braun A, Hanemann A, Ehehalt R, Autschbach, F, Karner M. Delayed release phosphatidylcholine in chronic-active ulcerative colitis: a randomized, double-blinded, dose finding study. J Clin Gastroenterol 2010;44:e101–e107. https://doi.org/10.1097/MCG.0b013e3181c29860

[31] Ehehalt R, Wagenblast J, Erben G, Lehmann WD, Hinz U, Merle U, Stremmel W. Phosphatidylcholine and lysophosphatidylcholine in intestinal mucus of ulcerative colitis patients. A quantitative approach by nanoElectrospray-tandem mass spectrometry. Scand J Gastroenterol 2004;39:737-42. https://doi.org/10.1080/00365520410006233

[32] Anes E, Kühnel MP, Bos E, Moniz-Pereira J, Habermann A, Griffiths G. Selected lipids activate phagosome actin assembly and maturation resulting in killing of pathogenic mycobacteria. Nat Cell Biol 2003;5:793-802. https://doi.org/10.1038/ncb1036

[33] Stremmel W, Ehehalt R, Autschbach F, Karner M. Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. Ann Intern Med 2007;147:603-10. https://doi.org/10.7326/0003-4819-147-9-200711060-00004

[34] Stremmel W, Merle U, Zahn A, Autschbach F, Hinz U, Ehehalt R. Retarded release phosphatidylcholine benefits patients with chronic active ulcerative colitis. Gut 2005;54:966-71. https://doi.org/10.1136/gut.2004.052316

[35] Cheng WD, Wold KJ, Benzoni NS, Thakwalakwa C, Maleta KM, Manary MJ, Trehan I. Lactoferrin and lysozyme to reduce environmental enteric dysfunction and stunting in Malawian children: study protocol for a randomized controlled trial. Trials 2017;18:523. https://doi.org/10.1186/s13063-017-2278-8

[36] Garas LC, Feltrin C, Hamilton MK, Hagey JV, Murray JD, Bertolini LR, Bertolini M, Raybould HE, Maga EA. Milk with and without lactoferrin can influence intestinal damage in a pig model of malnutrition. Food Funct 2016;7:665-78. https://doi.org/10.1039/c5fo01217a

[37] Kuwata H, Yamauchi K, Teraguchi S, Ushida Y, Shimokawa Y, Toida T, Hayasawa H. Functional fragments of ingested lactoferrin are resistant to proteolytic degradation in the gastrointestinal tract of adult rats. J Nutr 2001;131:2121-7. https://doi.org/10.1093/jn/131.8.2121

[38] Zavaleta N, Figueroa D, Rivera J, Sánchez J, Alfaro S, Lönnerdal B. Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea. J Pediatr Gastroenterol Nutr 2007;44:258-64. https://doi.org/10.1097/MPG.0b013e31802c41b7

[39] Cremon C, Stanghellini V, Barbaro MR, Cogliandro RF, Bellacosa L, Santos J, Vicario M, Pigrau M, Alonso Cotoner C, Lobo B, Azpiroz F, Bruley des Varannes S, Neunlist M, DeFilippis D, Iuvone T, Petrosino S, Di Marzo V, Barbara G. Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome. Aliment Pharmacol Ther 2017;45:909-22. https://doi.org/10.1111/apt.13958

[40] Aloe L, Leon A, Levi-Montalcini R. A proposed autacoid mechanism controlling mastocyte behaviour. Agents Actions 1993;39:C145-C147. https://doi.org/10.1007/BF01972748

[41] Kiani AK, Miggiano G, Aquilanti B, Velluti V, Matera G, Gagliardi L, Bertelli M. Food supplements based on palmitoylethanolamide plus hydroxytyrosol from olive tree or Bacopa monnieri extracts for neurological diseases. Acta Biomed 2020;91:e2020007. https://doi.org/10.23750/abm.v91i13-S.10582

[42] Rastegarpanah M, Malekzadeh R, Vahedi H, Mohammadi M, Elahi E, Chaharmahali M, Safarnavadeh T, Abdollahi M. A randomized, double blinded, placebo-controlled clinical trial of silymarin in ulcerative colitis. Chin J Integr Med 2015;21:902-6. https://doi.org/10.1007/s11655-012-1026-x

[43] Miroliaee AE, Esmaily H, Vaziri-Bami A, Baeeri M, Shahverdi AR, Abdollahi M. Amelioration of experimental colitis by a novel nanoselenium-silymarin mixture. Toxicol Mech Methods 2011;21:200-8. https://doi.org/10.3109/15376516.2010.547887

[44] Esmaily H, Vaziri-Bami A, Miroliaee AE, Baeeri M, Abdollahi M. The correlation between NF-κB inhibition and disease activity by coadministration of silibinin and ursodeoxycholic acid in experimental colitis. Fundam Clin Pharmacol 2011;25:723-33. https://doi.org/10.1111/j.1472-8206.2010.00893.x

[45] Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr 2002;21:495-505. https://doi.org/10.1080/07315724.2002.10719248

[46] Stenson WF, Cort D, Rodgers J, Burakoff R, DeSchryver-Kecskemeti K, Gramlich TL, Beeken W. Dietary supplementation with fish oil in ulcerative colitis. Ann Intern Med 1992;116:609-14. https://doi.org/10.7326/0003-4819-116-8-609

[47] Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 1996;334:1557-60. https://doi.org/10.1056/NEJM199606133342401

[48] Endres S, Lorenz R, Loeschke K. Lipid treatment of inflammatory bowel disease. Curr Opin Clin Nutr Metab Care 1999;2:117-20. https://doi.org/10.1097/00075197-199903000-00004

Correspondence: Gabriele Bonetti, MAGI'S LAB, Rovereto (TN), 38068, Italy. E-mail: gabriele.bonetti@assomagi.org

How to cite this article: Kiani AK, Bonetti G, Donato K, Bertelli M. Dietary supplements for intestinal inflammation. J Prev Med Hyg 2022;63(suppl.3):E214-E220. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2763