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THE ROLE OF DIETARY SUPPLEMENTS IN INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW

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Abstract

Recurrent episodes of gastrointestinal inflammation induced by an inappropriate immune response to gut bacteria characterize inflammatory bowel disease (IBD). The phrase "inflammatory bowel disease" refers to two distinct forms of idiopathic intestinal disease distinguished by their location and degree of gut wall involvement. Although Crohn disease is substantially more common in women than in men, ulcerative colitis appears to be equally common in both sexes. IBD is often frequent in affluent countries and cooler regions. It occurs when an excessively powerful immune response is generated in response to a normal stimulus, such as food or intestinal flora, in individuals who are genetically predisposed to developing the disorder. Diet significantly influences intestinal inflammation. Unbalanced meals can result in dysbiosis, which impairs the immune system of the host. The Mediterranean Diet is renowned for being anti-inflammatory and dysbiosis-preventing. Probiotics, butyrate, phosphatidylcholine, lactoferrin, palmitoylethanolamide, silymarin, and omega 3 should be introduced to the diet of the patient in order to stabilize the intestinal microbial population and reinforce the mucosal barrier, hence preventing or alleviating IBD symptoms. Intestinal inflammation is usually associated with vitamin D levels and gut flora. Constant study has demonstrated their link, therefore the prescription of probiotics and vitamin D is beneficial for IBD patients.

Keyword: *Dietary Supplements; Inflammatory Bowel Disease; Probiotics; Vitamin D levels*

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by recurrent episodes of gastrointestinal inflammation caused by an abnormal immune response to gut microflora. The term "inflammatory bowel disease" refers to two types of idiopathic intestinal disease that differ in their location and depth of involvement in the bowel wall.[1,2] Ulcerative colitis (UC) is characterized by widespread inflammation of the colonic mucosa. Crohn's disease (CD) causes transmural ulceration of any part of the gastrointestinal tract (GI), with the terminal ileum and colon being the most commonly affected. Both diseases are classified according to their severity (mild, moderate, or severe) and location. CD is also classified by phenotype, which can be inflammatory, stricturing, or penetrating.[3]

Inflammatory bowel disease (IBD) develops in genetically predisposed individuals as a result of an inappropriate immune response to intestinal flora. To this day, the cause of IBD is unknown. Many causes have been proposed, but none of them are universally present in all patients.[4] The one consistent feature of Crohn's disease is its association with tobacco. On the other hand, smoking appears to protect against ulcerative colitis. Diet's role is still being debated. The CARD15 gene has been linked to IBD, but due to its polymorphism, it is impossible to predict which part of the GI tract will be affected. Genes play a smaller role in ulcerative colitis than in Crohn's disease.[1]

The incidence of inflammatory bowel disease (IBD) in North America is between 2.2 and 19.2 cases per 100,000 person-years for ulcerative colitis and between 3.1 and 20.2 cases per 200,000 person-years for CD. The prevalence of adult ulcerative colitis in the United States was 238 per 100,000 population and 201 per 100,000 population, according to data from a large research based on insurance claims. IBD is significantly more frequent in North America and Europe compared to Asia and Africa. Although the majority of inflammatory bowel disease occurs in adults aged 15 to 30, up to 25% of patients will develop inflammatory bowel disease by adolescence. There appears to be a bimodal distribution with a second peak of 10 to 15 percent of individuals acquiring IBD around age 60.[5]

Although Crohn disease is significantly more prevalent in women than in men, ulcerative colitis appears to be equally prevalent in both sexes. IBD is typically prevalent in wealthy nations and cooler areas. It happens when an abnormally strong immune response is triggered in response to a typical stimulus, like food or intestinal flora, in those who are genetically predisposed to developing the condition. Food greatly affects intestinal inflammation. Unbalanced diets can cause dysbiosis, which disrupts the host immunological system. Anti-inflammatory and dysbiosis-preventing, the Mediterranean Diet is famous.[6,7]

Probiotics, butyrate, phosphatidylcholine, lactoferrin, palmitoylethanolamide, silymarin, and omega 3 should be added to the patient's diet to stabilize the intestinal microbial cohort and strengthen the mucosal barrier, preventing or relieving IBD symptoms. Nutritional supplements may reduce drug use's high costs, side effects, and relapses.[8–10] This article discusses the role of dietary supplements in inflammatory bowel disease.

METHODS

This study followed to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project guidelines for data collection, processing, and reporting. On the basis of these considerations, the adopted regulations were established. This literature review seeks to examine the function of dietary supplements in inflammatory bowel disease. These are the key concerns raised by the present investigation: 1) Articles must always be written in English and emphasize the role of dietary supplements in inflammatory bowel disease in order to be accepted for publication. 2) This evaluation examined articles published after 2015 but before the period covered by this systematic review. Editorials, submissions without a DOI, reviews of previously published articles, and entries that are substantially identical to those in the journal will not be included in the anthology.

The search for studies to be included in the systematic review was carried out from March, 17th 2023 using the PubMed and SagePub databases by inputting the words: “dietary supplements” and “inflammatory bowel disease”. Where *("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields]) AND ("inflammatory bowel diseases"[MeSH Terms] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "diseases"[All Fields]) OR "inflammatory bowel diseases"[All Fields] OR ("inflammatory"[All Fields] AND "bowel"[All Fields] AND "disease"[All Fields]) OR "inflammatory bowel disease"[All Fields])* is used as search keywords.

Each study's abstract and title were used to determine eligibility. Hence, historical literature is their main source. After reviewing many studies with the same results, unpublished English submissions are requested. The systematic review included only eligible studies. This limits search results to the specified criteria. Evaluation follows. The study analysis listed authors, publication dates, location, activities, and parameters. After saving search results in EndNote, duplicate articles were eliminated from the database. Two reviewers assessed each paper's title and abstract for relevance.

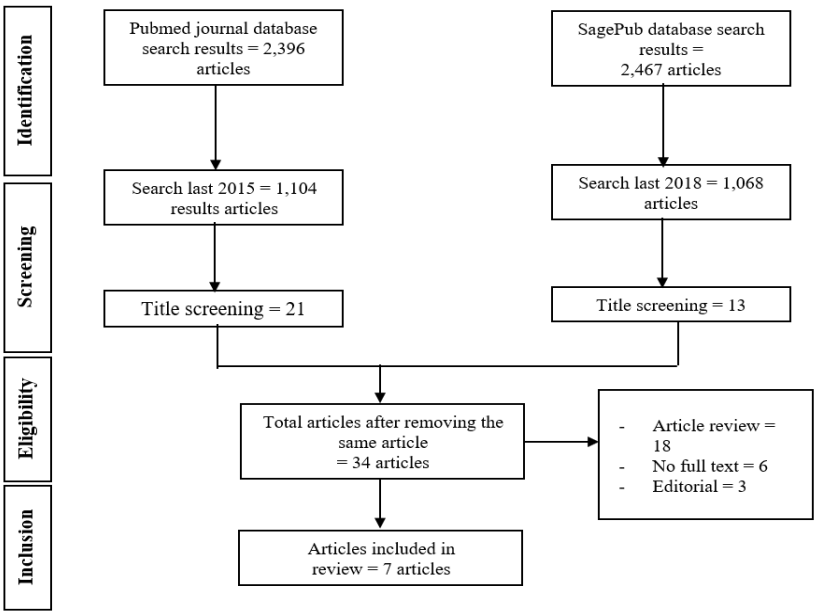

Figure 1. Article search flowchart

Before selecting papers to study, each author reviewed the title and abstract. Next, we'll examine all publications that meet the review's inclusion criteria. We will review relevant research publications after our research. This rule selects reviewable manuscripts. Selecting items for more investigation should be simpler. Which previous studies were included in the review, and why?

RESULT

First study about probiotic showed that *lactobacillus acidophilus* (LA-1) and *Pediococcus pentosaceus* decreased the generation of nitric oxide in RAW264.7 cells, however only LA-1 suppressed TNF-α and promoted Il10 expression. Inducing M2 macrophages in peritoneal cavity cells and Th2 and Treg cells in splenocytes, LA-1 lengthened the lifespan of dextran sulfate sodium-treated animals and diminished the severity of colitis. Induction of Il-10 expression and inhibition of pro-inflammatory cytokines accompanied the reconstitution of goblet cells in the colon. In addition, we discovered that LA-1 exhibits an anti-colitic effect by alleviating ER stress in both HT-29 cells and in vivo.

Second study in Italy conducted with 40 IBD patients were recruited and randomly assigned to take probiotics (test group, n=20) or placebo (control group, n=20) for 90 days. They showed that the results of the d-ROM assay made it abundantly evident that the values which were found in the test group had greatly improved, resulting in oxidative stress levels which were not pathological. Following the treatment of probiotics, the test group demonstrated rising BAP values, which provided conclusive evidence that the patients' general health had significantly improved.[11]

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Conclusion
Kim, 2019[13]	Republic of Korea	Clinical trial	Mouse colitis was induced using dextran sulfate sodium and confirmed by disease activity index and histology	They demonstrated that LA-1 has a significant ameliorating effect on ER stress and a dampening effect on NF-κβ activation. According to their findings, LA-1 has the potential to be utilized as an effective immunomodulator in the treatment of IBD, and the data also imply that the management of ER stress may have major consequences in the treatment of IBD.
Ballini, 2019[11]	Italy	Randomized Double-Blinded Placebo-Controlled	40 patients previously diagnosed for IBD	Patients with inflammatory bowel disease who took specific probiotics by mouth indicated that the supplements were both effective and safe.
Yilmaz, 2019[12]	Turkey	Randomized controlled trial	Forty-five patients with IBD were classified into two groups: 25 for treatment and 20 for control	According to the findings of their study, the consumption of kefir may alter the gut microbiota, and the frequent consumption of kefir may improve the quality of life of the patient in the short run.
Toscano, 2017[14]	Italy	Randomized controlled trial	Twenty Italian healthy volunteers were randomized in pre-prandial and post-prandial groups.	*L. kefiri* LKF01 demonstrated a high ability to change the composition of the gut microbiota, which resulted in a considerable reduction of a number of bacterial species directly engaged in the beginning of a pro-inflammatory response and gastrointestinal disorders.
Amrousy, 2021[15]	Egypt	Randomized double-blinded controlled clinical trial	120 children with IBD and hypovitaminosis D	It is possible that taking vitamin D supplements will help children who suffer from inflammatory bowel disease (IBD).
Palumbo, 2016[16]	Italy	Randomized double-blinded controlled clinical trial	Sixty patients with moderate-to-severe ulcerative colitis	In patients with mild to severe ulcerative colitis, a therapy paradigm consisting of anti-inflammatory medications and probiotics over an extended period of time is feasible and may be an alternative to corticosteroids.
Arihiro, 2019[17]	Japan	Randomized, double-blind, controlled trial	223 patients with IBD	Vitamin D supplementation may have a protective effect against upper respiratory infection in patients with IBD, but it may make the symptoms of UC worse.

Yilmaz, et al (2019)[12] study showed the total average count of lactic acid bacteria colony forming units in a kefir sample was 5 x 10^7 CFU/mL. All subjects in the treatment group had a Lactobacillus bacterial load of 104 to 10^9 CFU/g in their

feces, and the first and last measurements were statistically significant (p=0.001 in ulcerative colitis and p=0.005 in CD). The bacterial load of *L. kefiri* in the stool of 17 subjects ranged between 10^4 and 10^6 CFU/g. There was a significant decrease in erythrocyte sedimentation rate and C-reactive protein in CD patients, whereas hemoglobin increased, and bloating scores were significantly reduced (p = 0.012) and feeling good scores increased (p = 0.032) in the last 2 weeks.

Toscano, et al (2017)[14] was give probiotic administration for one month. They showed *L. kefiri* was recovered in the feces of all volunteers, but it was only discovered in the feces of three participants in the pre-prandial group and two subjects in the post-prandial group one month later. We noticed a drop in *Bilophila, Butyricicomonas, Flavonifactor, Oscillibacter,* and *Prevotella* after one month of probiotic use. *Bacteroides, Barnesiella, Butyricicomonas, Clostridium, Haemophilus, Oscillibacter, Salmonella, Streptococcus, Subdoligranolum,* and *Veillonella* were considerably reduced in post-probiotic samples compared to baseline samples. Palumbo, et al (2016)[16] showed every single patient who was given combination therapy exhibited greater improvement in comparison to the patients in the control group. Particularly, the advantageous benefits of probiotics continued to be visible even after two years of treatment.

Other study about vitamin D supplement showed supplementation significantly reduced IBD activity score. Furthermore, QOL improved significantly after vitamin D supplementation. In the vitamin D group, inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin, as well as interleukin-2 IL-12, IL-17, IL-23, and tumor necrosis factor-alpha, significantly decreased. IL-10, on the other hand, increased significantly after vitamin D supplementation. Vitamin D levels were significantly inversely related to the activity score, QOL score, levels of all inflammatory markers, hospitalization frequency, and emergency department visits.[15]

Other study was recruited 223 individuals suffering from IBD and randomly assigned them to one of two groups: those receiving vitamin D (n = 108) or placebo (n = 115). Nevertheless, those who took vitamin D had a significantly decreased incidence of upper respiratory infections (relative risk [RR] = 0.59; 95% confidence interval (CI), 0.35-0.98; P = 0.042). This effect was accentuated in the subgroup of participants with low levels of 25-OHD (RR = 0.36; 95% CI = 0.14-0.90; P = 0.02). The Lichtiger clinical activity index score was considerably lower in the vitamin D group when it came to adverse events (P = 0.002), and it only remained significantly lower in the high 25-OHD level subgroup.[17]

DISCUSSION

Probiotics

Numerous research have examined UC and CD microbiome alterations. Bacteroidetes and Firmicutes have been depleted, among other phyla. Microbial composition affects gut metabolites including butyrate and H2 S.[18] Probiotics, living microorganisms added to fermented meals, promote gut microbial stability and health. Probiotics immunomodulate the gut microbial population and diminish intestinal pathobionts such *Clostridium perfringens* and *Klebsiella pneumonia*.[10] Novel or next-generation probiotics, commensal organisms that reduce inflammation and restore the epithelial barrier, improve gut health.

De novo injection of certain microbial species to the gut as probiotic/bacterio-therapeutic preparations, dietary acceleration of gut species, or a combination of these strategies could achieve these goals. The main intestinal phyla are Lactobacilli, which reduce the quantity of toxin-producing intestinal bacteria and promote longevity, and *Bifidobacteria*, which maintain gut health with their secretions and extracellular structures. *Eubacterium hallii*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis* digest dietary fibers to fuel enterocytes and reduce gut inflammation. *Akkermansia muciniphila* improves metabolic syndrome and intestinal mucosa. Bacteroides species emit immunomodulatory compounds with additional benefits.[13,14,19]

L. pentosus, L. brevis, L. plantarum, L. fermentum, L. kefiri, and *L. lindneri* were isolated from kefir. The most common *lactobacilli isolated* from kefir grains as reported by other studies are: *L. brevis, L. kefir, Lactobacillus acidophilus, L. plantarum, L. kefiranofaciens, Lactobacillus kefirgranum,* and *Lactobacillus parakefiri*. *L. kefiri* strongly modulated gut microbiota composition, reducing numerous bacterial species directly engaged in proinflammatory response and GI disorders.[12] Terminal restriction fragment length polymorphism research demonstrated variations in the fecal microbiomes of UC and CD patients and healthy persons. Inactive UC patients have good intestinal microbiology. The intestinal processes and microbiota structure of these patients may help create new UC and CD treatments.[20]

Kim *et al*. supported probiotic supplementation in inflammatory bowel disease by showing that LA-1 significantly affects endoplasmic reticulum stress and suppresses the activation of NF-κβ (which leads to IBD pathogenesis) and could be used as a potential immunomodulator in IBD treatment.[13] Probiotics can help delay or prevent celiac disease, a common systemic condition affecting the small intestine caused by an inappropriate immune reaction to gluten. Probiotics regulate immunological response, toxin receptor degradation, nutrients competition, adhesion site blockage, and pathogen inhibitory chemicals.[21,22]

Vitamin D

Vitamin D supplementation was shown to have a considerable inhibitory effect on IBD activity levels as compared to the placebo group. In addition, the quality of life dramatically improved after vitamin D treatment was administered. Inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin, as well as

interleukin-2, IL-12, IL-17, IL-23, and tumor necrosis factor-alpha, fell by a substantial amount in the group that received vitamin D. On the other hand, a rise in IL-10 was observed following vitamin D administration.[15]

Vitamin D levels are inversely linked with mucosal inflammation and disease activity in IBD patients.[23] 34.5% of patients in the whole study population, 33.3% of patients with UC, and 38.1% of patients with CD had low vitamin D levels (25-OHD <20 ng/mL). There was no significant association between 25-OHD levels and disease activity. Reductions in 25-OHD have been associated with an increase in the incidence of upper respiratory infections, and vitamin D supplementation may mitigate this risk.[24] Taking a vitamin D supplement of 1,200 international units per day was preventative throughout the early period, but it was not effective during the later phase.[17]

The elevated amounts of 25-OHD did not appear to influence the serum concentrations of iPTH or calcium. Regarding IBD activity, the clinical activity score of UC patients receiving vitamin D treatment rose dramatically. However, there was a negligible rise; consequently, there was no need to alter the treatment for UC. This alteration was not observed in CD patients. The number of CD patients in this trial was insufficient to determine the effects of vitamin D on CDAI.[17]

Although this study's findings indicated that vitamin D supplementation had no effect on disease activity during the study period, additional research including significant numbers of individuals with CD is necessary to corroborate these findings. When providing vitamin D to patients with IBD, we urge that practitioners assess the patient's serum 25-OHD levels. If serum 25-OHD levels are adequate, doctors should be wary of any unfavorable side effects of supplementation. To examine the effect of vitamin D supplementation on patients with UC who do not have vitamin D insufficiency, additional research is required.[17]

CONCLUSION

Vitamin D levels and intestinal flora are frequently connected with intestinal inflammation. Consistent research has proven their association, therefore probiotic and vitamin D administration is advantageous for IBD patients.

REFERENCE

[1]. Dmochowska N, Wardill HR, Hughes PA. Advances in Imaging Specific Mediators of Inflammatory Bowel Disease. Int J Mol Sci. 2018 Aug;19(9).

[2]. Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.

[3]. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019 Feb;13(2):144–64.

[4]. Colombel J-F, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2019 Feb;17(3):380-390.e1.

[5]. Su H-J, Chiu Y-T, Chiu C-T, Lin Y-C, Wang C-Y, Hsieh J-Y, et al. Inflammatory bowel disease and its treatment in 2018: Global and Taiwanese status updates. J Formos Med Assoc. 2019 Jul;118(7):1083–92.

[6]. Ghishan FK, Kiela PR. Vitamins and minerals in inflammatory bowel disease. Gastroenterol Clin. 2017;46(4):797–808.

[7]. Chicco F, Magrì S, Cingolani A, Paduano D, Pesenti M, Zara F, et al. Multidimensional impact of Mediterranean diet on IBD patients. Inflamm Bowel Dis. 2021;27(1):1–9.

[8]. 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(12):1357–64.

[9]. Romani A, Ieri F, Urciuoli S, Noce A, Marrone G, Nediani C, et al. Health effects of phenolic compounds found in extra-virgin olive oil, by-products, and leaf of Olea europaea L. Nutrients. 2019;11(8):1776.

[10]. Vitetta L, Vitetta G, Hall S. Immunological tolerance and function: associations between intestinal bacteria, probiotics, prebiotics, and phages. Front Immunol. 2018;9:2240.

[11]. Ballini A, Santacroce L, Cantore S, Bottalico L, Dipalma G, Topi S, et al. Probiotics Efficacy on Oxidative Stress Values in Inflammatory Bowel Disease: A Randomized Double-Blinded Placebo-Controlled Pilot Study. Endocr Metab Immune Disord Drug Targets. 2019;19(3):373–81.

[12]. Yılmaz İ, Dolar ME, Özpınar H. Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: A randomized controlled trial. Turkish J Gastroenterol Off J Turkish Soc Gastroenterol. 2019 Mar;30(3):242–53.

[13]. Kim DH, Kim S, Lee JH, Kim JH, Che X, Ma HW, et al. Lactobacillus acidophilus suppresses intestinal inflammation by inhibiting endoplasmic reticulum stress. J Gastroenterol Hepatol. 2019;34(1):178–85.

[14]. Toscano M, De Grandi R, Miniello VL, Mattina R, Drago L. Ability of Lactobacillus kefiri LKF01 (DSM32079) to colonize the intestinal environment and modify the gut microbiota composition of healthy individuals. Dig liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2017 Mar;49(3):261–7.

[15]. El Amrousy D, El Ashry H, Hodeib H, Hassan S. Vitamin D in Children With Inflammatory Bowel Disease: A Randomized Controlled Clinical Trial. J Clin Gastroenterol. 2021 Oct;55(9):815–20.

[16]. Palumbo VD, Romeo M, Marino Gammazza A, Carini F, Damiani P, Damiano G, et al. The long-term effects of probiotics in the therapy of ulcerative colitis: A clinical study. Biomed Pap Med Fac Univ Palacky, Olomouc,

Czechoslov. 2016 Sep;160(3):372–7.
[17]. Arihiro S, Nakashima A, Matsuoka M, Suto S, Uchiyama K, Kato T, et al. Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza and Upper Respiratory Infection in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019 May;25(6):1088–95.
[18]. Lucas López R, Grande Burgos MJ, Gálvez A, Pérez Pulido R. The human gastrointestinal tract and oral microbiota in inflammatory bowel disease: a state of the science review. APMIS. 2017 Jan;125(1):3–10.
[19]. Abraham BP, Quigley EMM. Probiotics in Inflammatory Bowel Disease. Gastroenterol Clin North Am. 2017 Dec;46(4):769–82.
[20]. Andoh A, Imaeda H, Aomatsu T, Inatomi O, Bamba S, Sasaki M, et al. Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. J Gastroenterol. 2011 Apr;46(4):479–86.
[21]. Marasco G, Cirota GG, Rossini B, Lungaro L, Di Biase AR, Colecchia A, et al. Probiotics, Prebiotics and Other Dietary Supplements for Gut Microbiota Modulation in Celiac Disease Patients. Nutrients. 2020 Sep;12(9).
[22]. Vanderpool C, Yan F, Polk DB. Mechanisms of probiotic action: Implications for therapeutic applications in inflammatory bowel diseases. Inflamm Bowel Dis. 2008 Nov;14(11):1585–96.
[23]. Meckel K, Li YC, Lim J, Kocherginsky M, Weber C, Almoghrabi A, et al. Serum 25-hydroxyvitamin D concentration is inversely associated with mucosal inflammation in patients with ulcerative colitis. Am J Clin Nutr. 2016;104(1):113–20.
[24]. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. bmj. 2017;356.