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Diet as an epigenetic factor in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) has as a main characteristic the exacerbation of the immune system against enterocytes, compromising the individual's intestinal microbiota. This inflammatory cascade causes several nutritional deficiencies, which further compromise immunological functioning and, as a result, worsen the prognosis. This vicious cycle can be interrupted as the patient's dietary pattern meets their needs according to their clinical condition, acting directly on the inflammatory process of IBD through the interaction of food, intestinal microbiota, and epigenome. Specific nutritional intervention for IBD has a crucial role in pre-

venting and managing disease activity. This review addresses epigenetic modifications through dietary compounds as a mechanism for modulating the intestinal microbiota of patients with IBD.

Key Words: Inflammatory bowel disease; Epigenetics; Nutrition; Nutrigenetics

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Core Tip: Inflammatory bowel disease is an autoimmune disease that oscillates between phases of active disease and remission. In any of these situations there are epigenetic mechanisms involved, which are modified by lifestyle, with diet being one of the factors of epigenetic modulation.

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INTRODUCTION

Epigenetic modifications are heritable alterations in gene expression that do not involve changes in DNA sequence but affect how genes are turned on and off, modulating the risk and severity of many diseases, including inflammatory bowel disease (IBD)[1,2]; such modifications include DNA methylation, histone modifications, and non-coding RNA molecules [such as microRNAs (miRNAs)][3].

These epigenetic mechanisms can be activated and modified through the individual's genetic inheritance and/or environmental factors, including the individual's diet, which requires additional attention[4]. Alongside an exponential growth in IBD cases, we observe obesity and overweight individuals due to a Westernized diet, rich in sugars and fats but deficient in vitamins and minerals[5]. The nutritional status and disease lead to malnutrition, commonly observed in patients with IBD[6,7]. Given the role of diet as a modulator of epigenetic parameters in patients with IBD, this review aims to present some micronutrients and their importance in preventing and/or treating malnutrition in these individuals.

Epigenetics in the pathogenesis of IBD

Epigenetics is classically defined as the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence. However, this broad definition allows several mechanisms to be classified as epigenetic or 'above the genome'[4]. Some events are defined as fixed epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA molecules (such as miRNAs), which translate to phenotypes and can be transmitted down the cell lineage or across generations. These types of epigenetic preservations represent common patterns of epigenetic inheritance.

Environmental factors, including diet, gut microbiota composition, and exercise, can elicit phenotype changes through gene expression without changing the genetic sequence[8]. DNA methylation and histone modifications are two central epigenetic mechanisms that impact gene transcription and cell fate. On the other hand, the impact on the gene transcription and translation by non-coding RNAs, including miRNAs, is also linked to epigenetic control associated with a widely complex system of non-coding RNA regulation[9]. MiRNAs are a class of small, non-coding RNA molecules that play a crucial role in epigenetics. These tiny molecules, typically consisting of 18 to 25 nucleotides, do not encode proteins themselves but act as potent post-transcriptional regulators[10]. These small molecules can influence gene expression by binding to specific messenger RNA (mRNA) molecules, leading to either degradation or translational repression of the target mRNA. Through this mechanism, miRNAs can fine-tune the expression of a wide array of genes, thereby having significant control over various cellular processes[11].

The role of miRNAs in regulating transcriptional processes is paramount to maintaining cellular homeostasis and responding to external stimuli. When miRNAs bind to their target mRNA sequences, they prevent the translation of those mRNA molecules into functional proteins, effectively downregulating the expression of the corresponding genes. This regulation is essential in diverse biological phenomena, including development, cell proliferation, differentiation, and immune responses[12]. By modulating gene expression, miRNAs influence various signaling pathways and cellular networks, acting as crucial epigenetic regulators. Dysregulation of miRNAs has been associated with numerous diseases, such as cancer, gastrointestinal tract diseases, neurodegenerative disorders, and cardiovascular conditions, highlighting their significance in understanding the molecular basis of complex human biology[13].

DNA methylation is a genetic modification that influences gene activity through cytosine methylation and transformation at the 5-carbon position. Single-base resolution maps of DNA methylation in human cell lines indicate that approximately 5% of all cytosines are methylated under normal physiological conditions[14]. Cytosine methylation predominantly occurs in the CpG dinucleotides sequence, where the guanidine base follows methylated cytosines. The primary function of DNA methylation is to actively silence genes and DNA regions, repressing the gene transcription in

the gene promoter region by inhibiting the binding of transcription factors or transcriptional events[15]. The regulation of DNA methylation occurs by the *de novo* DNA methyltransferases DNMT3a and DNMT3b. Across cell divisions, DNA methylation events are maintained by DNMT1. Active removal of methyl groups from cytosines is also hypothesized to occur by specific but yet to be identified factors[15].

The mechanism of DNA methylation in IBD includes specific patterns such as global DNA hypomethylation. Studies have shown that patients with Crohn's disease (CD) and ulcerative colitis (UC) exhibit global DNA hypomethylation in various cell types, including intestinal epithelial cells and immune cells[16]. This hypomethylation can lead to genomic instability and altered gene expression, contributing to disease progression. On the other hand, promoter hypermethylation occurs when there is increased DNA methylation in specific promoter regions, which can result in gene silencing. Several genes involved in inflammation regulation, immune response, and epithelial barrier function in bowel diseases were found to be hypermethylated[17,18]. For example, genes encoding anti-inflammatory cytokines, such as interleukin-10, have been observed to have increased promoter methylation in IBD patients, potentially impairing their ability to control inflammation. However, some genes, including the nuclear transcription factor-kappa B signaling pathway, present hypomethylation status in IBD, leading to their overexpression, contributing to increased bowel inflammation[19].

In IBD patients, alterations in DNA methylation patterns have been identified in genes related to intestinal permeability, mucin production, and tight junction proteins[19,20]. These changes can disrupt the integrity of the gut barrier, leading to increased immune activation and inflammation.

Regarding histone modifications, another frequent epigenetic mechanism, the chromatin structure, has the function to protect and maintain the DNA organization. Histones are essential chromatin proteins and facilitate DNA packaging into nucleosomes[21]. Histone proteins can be subdivided into five major classes in humans (H1, H2A, H2B, H3, and H4), all of which possess tails that can be post-translationally modified to alter the accessibility of the DNA. Histone modifications include acetylation, methylation, phosphorylation, ADP-ribosylation, and ubiquitination in the histone tail which can occur mainly by lysine modifications[22]. The effect of histone modifications on transcription is highly diverse and depends on the type of modification, either silencing or activating gene transcription. Histone proteins and the adjacent tail can be modified to orchestrate DNA transcription, but the extension of this modification results in transcriptional activation or inactivation, depending on the type of modification[23]. Methylation of H3 is associated with transcriptional activation, whereas lysine 36 methylation results in transcriptional repression. Histone lysine acetylation activates gene transcription by histone lysine acetyltransferases (HATs), whereas histone deacetylases (HDACs) remove acetyl groups from lysine residues[22].

Phosphorylation of histone proteins at specific serine or threonine residues can affect gene expression by influencing chromatin structure and protein-protein interactions. In bowel diseases, abnormal histone phosphorylation events have been observed, particularly in inflammation. For instance, phosphorylation of histone H3 at serine 10 (H3S10ph) has been associated with increased expression of pro-inflammatory genes in colonic epithelial cells during colitis[24]. Regarding the histone acetylation pathways, inflammatory disturbances are mediated by the dysregulation of HDACs and HATs, directly impacting the balance of histone deacetylation and acetylation status. Increased expression and activity of HDACs have been observed in IBD, leading to histone deacetylation and transcriptional repression of anti-inflammatory genes, contributing to the perpetuation of chronic inflammation. On the other hand, reduced expression or function of HATs in IBD decreases histone acetylation, suppressing genes involved in maintaining intestinal barrier integrity, immune homeostasis, and immunoregulation[25]. Thus, altered activities of HDACs and HATs induce aberrant cytokine production, imbalanced T cell responses, and impaired epithelial barrier function in IBD, highlighting their crucial roles in disease pathogenesis[26].

In IBD, increased histone acetylation in certain gene promoters has also been observed, leading to the upregulation of pro-inflammatory genes, contributing to chronic inflammation[27]. Furthermore, alterations in histone methylation marks, such as H3K4me3 and H3K27me3, have been associated with altered gene expression profiles in the intestinal epithelium of patients with IBD[28].

It is important to note that specific histone modifications in IBD can vary depending on the individual, the disease subtype, and the stage. The effects of these modifications may depend on the genetic context and environmental factors, influencing several aspects of the pathophysiology of the disease, including inflammation, epithelial barrier integrity, and immune response.

Nutritional aspects of IBD

The incidence of IBD appears to be increasing worldwide in both developed and developing countries[6]. Today, 0.1% of Brazilians live with this chronic condition, as verified through the temporal analysis performed by Quaresma *et al*[29], which also showed a decrease in the incidence of CD but an increase in UC. Although we recognize genetic predisposition as a determining factor in the pathogenesis of IBD, other factors, such as environmental ones, are increasingly recognized as contributing to the risk of developing IBD. Notably, the incidence of IBD follows global trends in terms of lifestyle, industrialization, and the Western diet[7].

Alongside the rise of new cases of IBD in adults and children, malnutrition is also a prevalent nutritional characteristic, which varies from 65%-75% in CD and 18%-62% in UC. Furthermore, we often see overweight and obesity associated with malnutrition in patients with IBD.

This panorama regarding the nutritional condition of patients with IBD reflects the Westernized dietary pattern and the numerous deficiencies in the absorptive process and intestinal selectivity. Among the risk factors related to diet, the intake of ultra-processed foods, additives, and emulsifiers[30-32] is mentioned, since these reduce bacterial diversity and increase intestinal permeability and inflammatory mechanisms[33]. Considering these dietary risk factors associated with a higher incidence of IBD, it is important to prioritize preventive interventions through existing dietary guides, which

warn to avoid ultra-processed foods and increase the intake of fresh and minimally processed foods. The latter promotes diet-microbiome interaction through food groups and short-chain fatty acid (SCFA)-producing bacteria, which benefit from ingesting these foods, thus contributing to the necessary dietary changes in preventing IBD[33].

The key element that links diet to the emergence or worsening of IBD is dysbiosis. The chronic consumption of increased amounts of animal protein, saturated fats, and refined carbohydrates, a Westernized dietary pattern, results in dysbiosis and changes in the microbiota, with an increase in pathogenic bacteria, such as *Bacterioides spp.* and *Ruminococcus torques*[34].

Dysbiosis disrupts the intestinal barrier, making the mucous layer thinner and more permeable to pathogens and antigens, resulting in persistent inflammation. On the other hand, a diet rich in vegetables and fiber reduces intestinal pH and prevents the growth of potentially pathogenic bacteria, ensuring membrane selectivity[32].

People living with IBD should be encouraged to make dietary changes, as these play a significant role in the etiology and management of the disease, promoting the induction and maintenance of clinical remission associated with IBD therapies, in addition to preventing malnutrition and/or obesity, thus avoiding severe nutritional deficiencies, which compromise the course of the disease[35-38].

The most common nutritional deficiencies in IBD patients are folate and fat-soluble vitamins. Patients who undergo extensive bowel resection have an increased risk of vitamin B12 malabsorption. Other key micronutrients that can be deficient and should be monitored are calcium, selenium, magnesium, zinc, and iron[39,40].

Nutri-epigenetic modulator in IBD

Nutri-epigenetics is a field that explores the interaction between nutrition, gene expression, and disease development [41]. In the context of IBD, which includes conditions like CD and UC, there is emerging evidence suggesting that certain dietary factors can influence the epigenetic modifications that contribute to the development and progression of the disease. These modifications are believed to result from a complex interplay between environmental, immunological, and genetic factors[42] (Figure 1).

While diet alone may not be the underlying cause of IBD, it plays a crucial role in developing and managing this complex disease, significantly influencing the symptoms, flare-ups, and overall disease management[43]. Several dietary factors have been investigated in the context of IBD and their potential impact on epigenetic modifications, biased gene expression, and impact on health outcomes. Here are some critical points regarding diet as an epigenetic modulator of IBD (Table 1).

Methyl donor micronutrients

Certain nutrients found in the diet can act as methyl donors or cofactors for enzymes involved in epigenetic processes. Methyl donors provide methyl groups (-CH₃) for various biochemical reactions in the body, including DNA methylation, histone modifications, and RNA processing. These nutrients are involved in one-carbon metabolism and are crucial for maintaining proper epigenetic regulation, gene expression, and overall health[44,45]. Some essential methyl donor nutrients are discussed below.

Vitamin B9 (folate): Vitamin B9 (folate) is an essential water-soluble vitamin found in foods such as leafy green vegetables (spinach, cabbage, lettuce, and broccoli), legumes (bean, lentil, and pea), citrus fruits (orange and grapefruit), liver (chicken and beef), and fortified grains (wheat flour). Folate is an important component in metabolism and crucial in various biological processes, including DNA synthesis, repair, and methylation[46,47]. Regarding IBD, folate deficiency has been associated with alterations in DNA methylation patterns. Studies have shown that patients with IBD often exhibit lower levels of folate, and this deficiency can contribute to the dysregulation of DNA methylation in the intestinal epithelial cells[48]. Impaired methylation can lead to the aberrant expression of genes involved in inflammation, immune response, and intestinal barrier function, which are all critical aspects in the pathogenesis of IBD. By influencing DNA methylation, folate supplementation may restore usual gene expression patterns and improve the symptoms of IBD[49]. However, it is important to note that the relation between folate and IBD is complex, and the effects of folate supplementation may vary depending on individual factors. While folate deficiency can be detrimental, excessive folate intake may also have adverse effects, particularly in individuals with specific genetic variations.

Vitamin B12 (cobalamin): Vitamin B12 (cobalamin) is another water-soluble vitamin found primarily in animal-based foods like meat, fish (especially cold-water fish like salmon, trout, tuna, and sardines), shellfish, eggs, dairy products like milk, cheese, and yogurt, and fortified products like morning cereal and vegetable milk (soy, almond, or oat). Vitamin B12 contributes with folate to donate methyl groups for DNA methylation and other essential cellular processes[50].

Methionine: Methionine is an essential amino acid found in protein-rich foods such as meat, fish, eggs, seafood, nuts, soy-based food like tofu, legumes (beans, lentils, and chickpeas), dairy products, oats, and whole grains. It acts as a precursor for S-adenosylmethionine (SAM), the primary methyl donor for DNA and histone methylation[50]. SAM is a molecule formed from methionine and adenosine triphosphate. It is the primary methyl donor in numerous cellular processes, including DNA, RNA, protein, and histone methylation[51].

Betaine (trimethylglycine): Betaine (trimethylglycine) is a naturally occurring compound found in foods like beets, spinach, broccoli, shellfish, and whole grains (wheat and rye) that acts as a methyl donor in reactions that convert homocysteine to methionine, which can be used for DNA and protein methylation[52].

Choline: Choline is an important nutrient involved in various biological processes, including lipid metabolism and cell membrane structure. Choline can be converted to betaine, and both choline and betaine behave as methyl donors in the

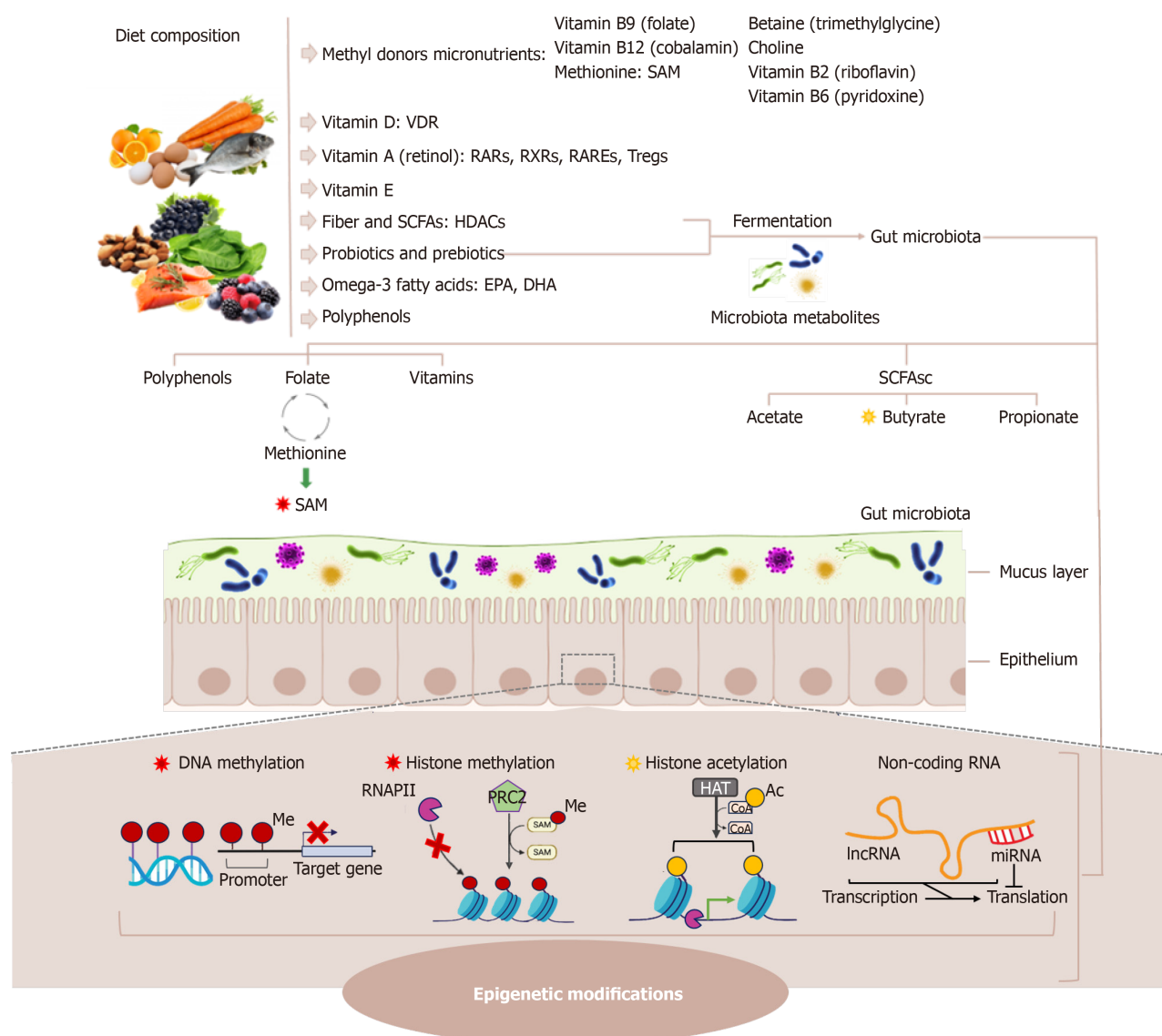
Table 1 Nutrients and their effect on epigenetic modifications in the context of inflammatory bowel disease

Nutrient(s)	Dietary sources	Biological activities	Epigenetic modifications	Ref.
Vitamin B (folate)	Leafy green vegetables, legumes, citrus fruits, and fortified grains	Methyl donor, DNA synthesis and repair	DNA methylation	[47-50]
Vitamin B12 (cobalamin)	Animal-based foods like meat, fish, eggs, and dairy products	Methyl donor	DNA methylation	[51]
Methionine	Protein-rich foods such as meat, fish, and dairy products	Methyl donor	DNA and histone methylation	[51, 52]
Betaine (trimethylglycine)	Beets, spinach, and whole grains	Methyl donor	DNA and protein methylation	[53]
Choline	Eggs, liver, peanuts, and cruciferous vegetables	Methyl donor, lipid metabolism, and cell membrane structure	DNA methylation	[53]
Vitamins B2 (riboflavin) and B6 (pyridoxine)	Whole grains, nuts, seeds, poultry, fish, and leafy green	FAD and FMN precursors	DNA methylation	[54]
Vitamin D	Fatty fish, eggs	VDRs ligand	DNA and histone methylation	[55-60]
Vitamin A	Leafy green vegetables, orange and yellow vegetables, tomato, fruits, and vegetable oils	RARs and RXRs ligand	DNA methylation, histone methylation and acetylation	[61-64]
Vitamin E	Plant-based oils, nuts, seeds, fruits, and vegetables	Antioxidant	DNA and histone methylation	[64-68]
SCFAs	High-fiber diets	Inhibition of HDACs activity	Histone acetylation	[69-73]
<i>Lactobacillus rhamnosus</i> GG	Fermented foods	Anti-inflammatory	DNA methylation	[78]
EPA and DHA	Salmon, mackerel, and sardines, flaxseeds, and walnuts	Anti-inflammatory	DNA methylation, histone methylation and acetylation, non-coding RNA	[81-83]
Polyphenols	Plant-based foods, such as fruits (berries), vegetables, nuts, seeds, green tea, cocoa, and olive oil	Anti-inflammatory and antioxidant	DNA methylation and non-coding RNA	[84, 85]

FAD: Flavin adenine dinucleotide; FMN: Flavin mononucleotide; VDRs: Vitamin D receptors; RARs: Retinoic acid receptors; RXRs: Retinoid X receptors; SCFAs: Short-chain fatty acids; HDACs: Histone deacetylases; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

body. Good sources of choline include eggs, liver, cold-water fish such as salmon and tuna, peanuts, dairy products, walnuts, almonds, sunflower seeds, and cruciferous vegetables[52].

Vitamins B2 (riboflavin) and B6 (pyridoxine): Vitamins B2 (riboflavin) and B6 (pyridoxine) are not primary donors like folate, vitamin B12, betaine, or choline, but they indirectly contribute to one-carbon metabolism and influence methylation reactions. B2 is an essential water-soluble vitamin, as it is a precursor for two important coenzymes, flavin adenine dinucleotide and flavin mononucleotide. These coenzymes are involved in redox reactions, energy metabolism, and various enzymatic reactions, including those related to the methylation process. Moreover, B2 plays an indirect role by synthesizing and recycling the methyl donor methionine. Conversion of homocysteine to methionine requires a methyl group from 5-methyltetrahydrofolate derived from folate metabolism. Additionally, vitamin B2 is necessary for converting folate to its active form, 5-methyltetrahydrofolate, thus indirectly supporting one-carbon metabolism and methylation reactions. Regarding B6, it represents a group of water-soluble compounds that include pyridoxine, pyridoxal, and pyridoxamine. These compounds are converted to their active form, pyridoxal 5'-phosphate (PLP), in the body. PLP is a coenzyme involved in various enzymatic reactions, including those related to amino acid metabolism. Similar to B2, vitamin B6 indirectly supports methylation reactions by converting methionine to SAM, the primary methyl donor for DNA and histone methylation. PLP is specifically required for the enzymatic reaction that converts methionine to SAM. Hence, a balanced diet that includes sources of B2 and B6, such as whole grains, nuts, seeds, avocado, potatoes, banana, dairy products, poultry, fish, and leafy green[45] vegetables, can help ensure sufficient levels of these nutrients [45]. Although methyl donors can alter DNA methylation patterns, little is known about the necessary doses and the exact period of dietary exposure or depletion that contributes to changes in epigenetic marks[45]. Therefore, more systematic studies are needed to provide more consistent findings.



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Figure 1 Schematic representation of the interplay of specific dietary constituents with the gut microbiota that interacts with the mammalian epigenome through the production of epigenetic substrates or regulators of chromatin-modifying enzymes. This process leads to epigenetic modifications that affect the immune response, compromising the epithelial barrier and defense mechanisms, resulting in chronic inflammation, as observed in inflammatory bowel disease. VDR: Vitamin D receptor; SCFAs: Short-chain fatty acids; HDACs: Histone deacetylases; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; RARs: Retinoic acid receptors; RXRs: Retinoid X receptors; RAREs: Retinoic acid response elements; Tregs: Regulatory T cells.

VITAMIN D

Vitamin D is a fat-soluble vitamin that is crucial in various physiological processes. Adequate levels of vitamin D, which can be obtained through sun exposure and dietary sources like fatty fish, cod liver oil, eggs, liver, and fortified foods (milk, orange juice, and morning cereals), have been linked to a lower risk of IBD[53,54]. Growing evidence suggests that vitamin D can affect DNA methylation patterns and histone modifications, leading to changes in gene expression profiles. Vitamin D acts as a ligand for the vitamin D receptor (VDR), which is present in various cell types, including immune cells. Upon binding to the VDR, vitamin D can influence the activity of enzymes involved in DNA methylation and histone modification, thereby altering gene expression[55,56].

Recent findings demonstrated that vitamin D deficiency is prevalent in individuals with IBD, and low vitamin D levels have been associated with increased disease activity and a higher risk of flare-ups[57]. Supplementing vitamin D in IBD patients has been shown to benefit disease activity and reduce inflammation. Furthermore, studies revealed that vitamin D supplementation can modulate epigenetic processes, altering IBD patients' DNA methylation patterns in immune cells and intestinal tissues. Thus, these changes in DNA methylation can affect the expression of genes involved in inflammation and immune regulation[58]. However, the exact mechanisms through which vitamin D influences epigenetic processes in IBD are still being elucidated.

VITAMIN A

Vitamin A, also known as retinol, is a crucial nutrient that plays a significant role in various biological processes, including immune function and inflammation. This fat-soluble vitamin is found in the form of beta-carotene in food sources like liver, carrots, sweet potato, pumpkin, spinach, kale, mango, melon, egg yolks, fatty fish, dairy products, and other orange vegetables (peppers and yellow zucchini). Their effects on gene expression through both genomic and non-genomic pathways were already demonstrated previously[59]. Retinoic acid, the active form of vitamin A, acts as a ligand for nuclear receptors known as retinoic acid receptors and retinoid X receptors. When retinoic acid binds to these receptors, it can regulate gene expression by interacting with specific DNA sequences called retinoic acid response elements in the promoter regions of targeted genes[60].

Recent findings demonstrated that retinoic acid affects DNA methylation patterns, leading to changes in gene expression profiles associated with immune regulation and inflammation. Additionally, retinoic acid can influence histone modifications, such as acetylation and methylation, which can further impact gene expression and cellular processes involved in IBD[61]. Furthermore, vitamin A has been shown to promote the development and function of regulatory T cells (Tregs) in the gut. Tregs are crucial in maintaining immune tolerance and preventing excessive inflammatory responses. Vitamin A helps to induce the expression of the transcription factor Foxp3, which is essential for Treg development and function. Epigenetic modifications, including DNA methylation and histone modifications, have been implicated in regulating Foxp3 expression and Treg function[62]. The therapeutic benefits of vitamin A as an epigenetic modulator, concerning its continuous use as a nutritional supplement, depend on our further understanding of its epigenetic effects on health and disease through different generations.

VITAMIN E

Vitamin E is a fat-soluble vitamin with antioxidant properties that protects cells from oxidative damage. While vitamin E is primarily known for its antioxidant effects, it also has some influence on epigenetic processes[62]. There were limited direct studies on the influence of vitamin E on epigenetic processes in IBD. However, research in other contexts suggests that vitamin E could impact epigenetic mechanisms.

Some studies in different disease models and cellular systems have shown that vitamin E can affect DNA methylation and histone modifications, both of which are crucial epigenetic mechanisms. These changes in epigenetic marks could lead to altered gene expression patterns and potentially influence disease processes[63-66].

While these studies provide preliminary evidence of the potential influence of vitamin E on epigenetic processes in IBD, additional research is needed to fully understand the mechanisms involved and establish a clear cause-and-effect association. Further studies, including clinical trials, are necessary to determine the optimal dosage and period of vitamin E supplementation and its effects on epigenetic modifications in individuals with IBD. It is important to emphasize that vitamin E supplementation should be approached with caution, especially at high doses, as excessive intake may have adverse effects. On the other hand, the consumption of foods rich in vitamin E can be encouraged, such as sunflower seeds, almonds, nuts, vegetable oils (wheat oil, sunflower oil, and wheat germ oil), avocado, hazelnuts, salmon, kiwi, mango, and tomatoes.

Fiber and SCFAs

High-fiber diets have been associated with several beneficial effects in IBD, such as reduced inflammation, improved gut barrier function, and modulation of the gut microbiota[67]. Soluble fiber can dissolve in water, forming thick gels, and is subject to fermentation by colonic bacteria. Examples of highly fermentable soluble fibers with significant solubility and viscosity are beta-glucans and pectin, naturally present in whole grains like oats and barley and fruits such as apples. Non-viscous soluble fibers that undergo fermentation by the gut microbiota include inulin, gum acacia, resistant starch, polydextrose, and corn fiber. Fructans of the inulin-type are naturally found in agave (a succulent plant), artichokes, asparagus, bananas, chicory root, garlic, onions, and leeks. Resistant starches (found in legumes, seeds, raw and cooked potatoes, green bananas, and whole grains) and polydextrose are not absorbed in the small intestine due to their specific physical and chemical characteristics, rendering them inaccessible to α -amylase[35].

One of the mechanisms by which high-fiber diets can influence epigenetic processes is the production of SCFAs. SCFAs are generated by the fermentation of dietary fiber by gut bacteria, such as butyrate, propionate, and acetate. They have been shown to have anti-inflammatory effects and can act as signaling molecules that modulate gene expression through epigenetic modifications[28].

Butyrate, a type of SCFA, has been shown to inhibit the activity of HDACs, enzymes involved in epigenetic regulation. HDACs remove acetyl groups from histone proteins, leading to a more condensed chromatin structure and reduced gene expression. By inhibiting HDACs, butyrate and other SCFAs can promote a more relaxed chromatin structure, allowing increased gene expression of anti-inflammatory genes[62,28,68]. Furthermore, high-fiber diets can also influence the gut microbiota composition. Certain beneficial bacteria in the gut, such as *Faecalibacterium prausnitzii*, have been associated with the production of anti-inflammatory metabolites and a healthy gut environment[69,70].

Probiotics and prebiotics

Probiotics are live microorganisms that can be consumed through fermented foods or supplements and, when administered in adequate amounts, provide health benefits to the host. Some foods are naturally rich in probiotics or are fermented to contain these microorganisms like yogurt, kefir, kimchi, sauerkraut, pickles, aged cheese, and some

fermented soy products such as miso and tempeh. Probiotics have been extensively studied for their potential therapeutic effects in various health conditions, including IBD. While probiotics have shown promise in improving symptoms and reducing inflammation in IBD, their specific influence on epigenetic processes in this context is an area of ongoing research[71].

Some studies have explored the effects of probiotics on epigenetic modifications in the context of IBD. They found that the probiotic treatment led to changes in DNA methylation patterns at specific gene loci, suggesting a potential epigenetic mechanism underlying the beneficial effects of probiotics in IBD[72-74].

Other studies evaluated the effects of a specific probiotic strain, *Lactobacillus rhamnosus* GG, on DNA methylation patterns in a mouse model of colitis. They observed that the probiotic treatment altered DNA methylation in the colon tissue, potentially contributing to its anti-inflammatory effects[75].

Although these studies provide insights into the potential epigenetic effects of probiotics in IBD, it is important to note that the exact mechanisms by which probiotics influence epigenetic processes are still not fully understood. Further research is needed to elucidate the specific molecular pathways involved to determine the clinical implications of these findings.

In addition to probiotics, there also are prebiotics, which are non-digestible fibers that promote the growth of beneficial gut bacteria. Both have shown promise in modulating epigenetic processes and reducing inflammation associated with IBD[76]. A recent review showed that dietary prebiotics, as well as their microbial metabolites, directly target enzymatic activities and/or modulate the expression of enzymes involved in epigenetic gene regulation, with potential implications for health status and susceptibility to diseases[77].

Although the exact mechanisms by which prebiotics influence epigenetic processes in IBD are not yet fully understood, these studies provide evidence of their potential to modulate gene expression through epigenetic modifications. Further research is needed to elucidate the specific mechanisms and identify the most effective prebiotic interventions for individuals with IBD.

Omega-3 fatty acids

Omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, are polyunsaturated fatty acids commonly found in fatty fish (such as salmon, mackerel, and sardines), flaxseeds, and walnuts. They have anti-inflammatory properties and have been studied for their potential therapeutic effects on IBD. Several studies have indicated that omega-3 fatty acids can modulate epigenetic processes associated with inflammation in IBD by reducing DNA methylation, potentially upregulating the expression of anti-inflammatory genes and downregulating the expression of pro-inflammatory genes, leading to beneficial effects on IBD[78,79].

In addition to DNA methylation, omega-3 fatty acids can also affect other epigenetic mechanisms, such as histone modifications and expression of miRNAs, which are small RNA molecules that can post-transcriptionally regulate gene expression, although the specific mechanisms are still being investigated[80].

Overall, omega-3 fatty acids have the potential to modulate epigenetic processes in IBD, leading to reduced inflammation and improved outcomes. However, further research is needed to fully understand the precise mechanisms and determine the optimal dosages and treatment strategies for using omega-3 fatty acids in managing IBD.

Polyphenols

Polyphenols are a group of bioactive compounds found in various plant-based foods, such as fruits (berries, apple, and grape), green leafy vegetables (spinach, kale, and broccoli), onion, garlic, nuts, hazelnuts, almonds, seeds, green tea, black tea, coffee, cocoa, whole grains (oats, barley, and buckwheat), and olive oil. These compounds have been studied for their potential health benefits, including their ability to modulate epigenetic processes and potentially exert beneficial effects in IBD.

These compounds have been shown to have anti-inflammatory and antioxidant properties, and they can modulate various signaling pathways involved in immune response and inflammation. One of the well-studied epigenetic effects of polyphenols is their ability to influence DNA methylation. Polyphenols can affect DNA methyltransferase enzymes, which are responsible for adding or removing methyl groups from DNA molecules. By modulating these enzymes, polyphenols can potentially alter DNA methylation patterns, leading to changes in gene expression[81,82].

Moreover, polyphenols can also affect histone modifications, which regulate chromatin structure and gene expression. They can influence enzymes responsible for adding or removing acetyl, methyl, or other chemical groups to histone proteins, thereby modulating the accessibility of DNA and influencing gene expression patterns. Additionally, polyphenols have been shown to regulate the expression of miRNAs[83-85].

While promising evidence suggests the epigenetic influence of polyphenols in IBD, it is important to note that research in this area is still evolving, and more studies are needed to fully understand the specific mechanisms and effects of different polyphenols in IBD. It is important to note that the field of nutri-epigenetics in IBD is still in its early stages. Understanding the interplay between dietary factors and epigenetic mechanisms in IBD is an active area of research. While evidence suggests their involvement, more studies are needed to elucidate the specific mechanisms and determine the potential therapeutic implications of targeting these factors in managing IBD. It is essential for individuals with IBD to work closely with healthcare professionals, such as gastroenterologists and registered dietitians, to ensure optimal nutrient intake and personalized management strategies.

CONCLUSION

In conclusion, evidence has shown that dietary composition should be the primary basis for managing patients with IBD due to its role in intestinal health. Moreover, the impact of diet on the epigenetic process of microbiota modulation is clear. However, further clinical trials involving diets, supplements, and epigenetic and inflammatory markers are still needed.

FOOTNOTES

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