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[1] Department of Internal Medicine, Medical School, São Paulo State University (Unesp), Botucatu 18618-686, São Paulo, Brazil

[2] Institute of Biosciences, São Paulo State University (Unesp), Botucatu 18618-686, São Paulo, Brazil

[3] Department of Internal Medicine, School of Medical Sciences, University of Campinas, CEP 13083-887 Campinas, SP, Brazil

[4] Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Department of Clinical Medicine, Aalborg University (AAU), Copenhagen, Denmark

[5] Department of Surgery, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

[*] Correspondence: danimagro06@gmail.com; Tel.: +55 (19) 35219450

[†] These authors contributed equally to this work.

Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic conditions marked by dysregulated inflammation in the gastrointestinal tract. Although the pathophysiology of IBD remains incompletely understood, it involves complex interactions between genetic predisposition and environmental triggers, such as gut microbiota imbalances and immune dysfunction, leading to chronic inflammation and mucosal injury. IBD affects approximately 7 million individuals globally, with prevalence increasing in Europe, North America and Oceania. This rise parallels the growing consumption of ultra-processed foods (UPF), which are typically rich in sugars, fats, and additives but low in fiber, vitamins, and other essential nutrients. High UPF consumption is associated with intestinal dysbiosis, marked by reduced microbial diversity, decreased short-chain fatty acid production, impaired barrier integrity, and mucus layer disruption. These alterations may promote immune-mediated diseases, including IBD, where dysbiosis is often characterized by an overgrowth of pathogenic bacteria such as *Clostridium* and *Enterococcus*, ultimately triggering inflammatory responses in the host. Considering these associations, this review critically examines the influence of UPF consumption on gut microbiota composition and function, and its potential link to IBD.

Keywords: ultra-processed food; gut microbiota; Crohn's disease; ulcerative colitis; inflammatory bowel disease

1. Introduction

Over the years, various methods of obtaining, preserving, and preparing food have been developed to ensure survival in adverse environmental conditions. [1] The transition from nomadic societies to agricultural communities marked the beginning of a more direct relationship with food production, primarily based on minimally processed and seasonal ingredients. The Industrial Revolution brought about a profound transformation in production, distribution, and consumption of food. The emergence of preservation, refining, and industrialization technologies enabled large-

scale production and the creation of products with extended shelf life, enhanced convenience, and increased palatability. However, these advancements have shifted dietary patterns away from traditional diets and increased reliance on highly processed foods. [1–3]

In recent decades, this phenomenon has intensified, particularly in developed countries and increasingly in developing nations, leading to the widespread adoption of Westernized dietary patterns. [3] These patterns are characterized by a high consumption of sugars, saturated fats, chemical additives, and ultra-processed foods (UPF). This significant dietary shift, coupled with an increasingly sedentary lifestyle, has been directly implicated in the escalating prevalence of non-communicable chronic diseases (NCDs), including type 2 diabetes, obesity, cardiovascular diseases, cancer, and various intestinal disorders. [4–7] Among these conditions, inflammatory bowel diseases (IBD) are particularly notable, with incidence rising alarmingly even in regions historically characterized by low prevalence, such as Latin America, Asia, and Africa. [8] The etiopathogenesis of IBD is multifactorial, involving genetic predisposition, immunological alterations, environmental factors, and, critically, gut microbiota dysbiosis. [3,9] The observed rise in IBD incidence is occurring concurrently with the increased intake of UPF across various countries. [10]

Considering this compelling evidence and the global impact of UPF consumption, this review aims to describe the role of UPF in the development of inflammatory bowel disease, explore its implications for gut microbiota composition and function, and discuss its potential associations with IBD risk.

2. Ultra-Processed Foods

According to the NOVA classification, UPF is an industrial formulation made from food-derived ingredients or synthesized in laboratories. UPF often contain additives such as emulsifiers, sweeteners, preservatives, and colorants, and may include components of natural foods, all of which are characterized by a high degree of processing. [11,12] (Figure 1)
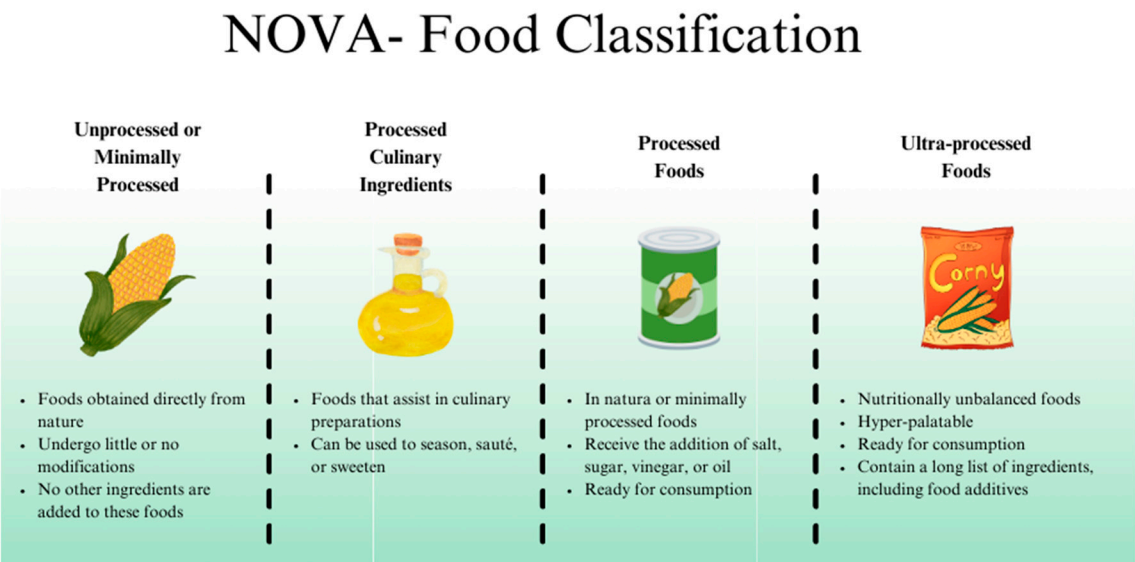
Figure 1. NOVA classification of foods. [11].

UPF accounts for up to 58% of daily caloric intake in high-income countries and approximately 30% in emerging economies. This widespread availability and consumption, particularly since the 1970s, coincides with a rise in NCDs, including IBD. [13] These products, such as industrial sweets, snacks, breads, cereals, margarines, processed meats, soft drinks, boxed juices, and industrial alcoholic beverages, are nutritionally imbalanced, highly palatable, and easy to consume. Their high

content of refined sugars, fats (especially n-6 polyunsaturated fatty acids), and low fiber content have been identified as risk factors for the development of IBD. [4,7] Another significant concern is the use of food additives. Substances like stabilizers, colorants, and emulsifiers are added to alter foods' physical, chemical, and sensory characteristics. Although approved by regulatory agencies, these compounds have been associated with alterations in the composition and function of the gut microbiota. [14]

While UPF are associated with microbial imbalances and increased intestinal inflammation, diets rich in fiber and minimally processed foods promote greater microbial diversity, playing a role in preventing chronic inflammatory diseases. Thus, the increasing consumption of UPF, paralleling the rising incidence of IBD in many countries, raises serious concerns about their impacts on gut health and systemic inflammation. [10]

3. Impact of Ultra-Processed Foods on Gut Microbiota and Intestinal Homeostasis

The gut microbiota plays a vital role in human health, constantly adapting to its intestinal environment. It provides numerous physiological benefits in a "healthy state", known as eubiosis or normobiosis. These processes include metabolizing dietary nutrients, fermenting prebiotic fibers, synthesizing vitamins B and K, secreting antimicrobial compounds, modulating immune responses, and maintaining the integrity of the intestinal epithelial barrier to prevent pathogen adhesion and colonization. [15,16] However, the consumption of UPF is consistently linked to significant alterations in gut microbiome composition and low-grade inflammation. Specifically, an increase in microbial taxa associated with obesity and metabolic disorders is observed, alongside a decline in beneficial groups like *Bacteroides, Verrucomicrobia, Eubacterium rectale, Coprococcus coccoides*, and *Bifidobacterium*. This dysbiotic shift often produces a proportional rise in pro-inflammatory phyla such as Bacillota and Pseudomonadota. This imbalance, coupled with elevated pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrosis Factor (TNF-α)) and lipopolysaccharides (LPS), drives processes such as hyperinsulinemia, adipogenesis, and hepatic steatosis. [17,18]

The persistent low-grade inflammation driven by UPF consumption can also lead to a "leaky gut" or increased intestinal permeability. [5,19] This compromised barrier then facilitates the translocation of pathogenic bacteria and LPS into the bloodstream, significantly exacerbating the inflammatory response observed in IBD. LPS plays a central role by activating the innate immune system, triggering the recruitment of macrophages, neutrophils, and dendritic cells through Toll-Like Receptor (TLR) signaling, which in turn releases key pro-inflammatory mediators, such as IL-1α, IL-1β, TNF-α, and IL-6. [5,19,20] For instance, serum LPS levels are reportedly six times higher in patients with active Crohn's disease (CD) compared to healthy controls, highlighting its potential to intensify CD-related inflammation. [21] Some studies suggest that the IL-23/IL-17 axis, central to CD pathogenesis, may increase the intestinal epithelium's susceptibility to LPS exposure, further exacerbating inflammation. [22] While the evidence directly linking UPF to UC is less consistent—possibly due to its complex pathogenesis—circulating LPS may still act as a precursor in UC progression. [23]

Beyond LPS, flagellin levels have also been associated with CD inflammation and intestinal barrier integrity. [24] Although its exact mechanism is not fully elucidated, the hypothesis linking flagellin to CD pathogenesis suggests it may drive T-cell and B-cell immune responses, potentially arising from compromised transepithelial electrical resistance to pro-inflammatory cytokines after flagellin exposure, leading to reduced tight junction proteins. [25]

4. Impact of Food Additives on Gut Microbiota

Food additives, commonly found in UPF, are designed to enhance product characteristics and extend shelf life. However, a growing body of evidence indicates they can profoundly impact gut microbiota composition and function, thereby contributing to intestinal inflammation and dysbiosis.

Studies in both humans and animals show that these additives can trigger pro-inflammatory changes in the microbiota, enhance LPS release, disrupt the production of beneficial metabolites like short-chain fatty acids (SCFAs), and impair the mucus layer and β-defensin expression. [26–28] Indeed, diets in which UPF constitutes over 20% of total daily caloric intake may compromise mucus barrier integrity, impair goblet cell function, and increase the risk of disease. [29] (Table 1).

Table 1. Summary of studies on food additives and the risk of gut disease.

Study (year)	Model	Additive(s)	Key Findings Related to Gut Microbiota/Health
Suez et al., 2014 [30]	Germ-free mice	Non-caloric artificial sweeteners (NAS)	Excessive consumption may promote glucose intolerance, dysbiosis, and metabolic alteration.
Araújo, 2017 [31]	Humans, ages 18-60 years	Carboxymethylcellulose (CMC)	Increased bacterial proliferation and infiltration, with an increase in Roseburia spp. and Lachnospiraceae bacterium species.
Laudisi, 2018 [32]	Mice	Maltodextrin	Decreased Muc-2 results in greater adhesion of pathogenic bacteria.
Pinget et al., 2019 [33]	Mice	Titanium Dioxide (TiO_2)	TiO_2 may impair intestinal homeostasis, increase inflammatory cytokine expression, and decrease crypt length.
He et al., 2021 [34]	Mice	Colorants Red 40 and Yellow 6	It can intensify intestinal inflammation and induce colitis.
Silva, 2022 [35]	Wistar rats	Xanthan gum	Continuous consumption increases pro-inflammatory cytokines (TNF-α, IL-6, and IL-10) and alters intestinal barrier integrity.
Chassaing et al., 2022 [36]	Humans, 16 adults	Carboxymethylcellulose (CMC)	Alteration in gut microbiota composition and reduction of metabolites like SCFAs.
Sieg et al., 2024 [37]	In vitro	Iron oxide food colorants (E 172)	E 172 showed strong interaction with intestinal cells, though no toxic effects were observed.
Han et al., 2025 [38]	In vitro	Carrageenan	Degraded carrageenan generates pro-inflammatory cytokines, such as IL1-b and TNF-a, which are related to the development of IBD.

4.1. Emulsifiers

In vitro study utilizing fecal samples from healthy individuals has investigated the effects of common emulsifiers dietary on the gut microbiome, including propylene glycol monostearate (PGMS) and sodium stearoyl lactylate (SSL). These latter two, frequently found in kinds of margarine, baked goods, and desserts, significantly reduced butyrate-producing families such as *Clostridiaceae*, *Lachnospiraceae,* and *Ruminococcaceae,* while increasing *Bacteroidaceae* and *Enterobacteriaceae*. SSL was also linked to elevated LPS and flagellin levels, possibly due to increased production by Escherichia. [39]

Specifically, carboxymethylcellulose (CMC) may promote bacterial adherence to the intestinal epithelium, facilitating bacterial proliferation and infiltration between intestinal villi. It can also alter the gut microbial composition, decreasing beneficial species such as *Faecalibacterium prausnitzii* and *Ruminococcus* spp. (both associated with SCFA production), while increasing *Roseburia* spp. and Lachnospiraceae bacterium. [31,36] Furthermore, consuming CMC and the emulsifier polysorbate 80 (P80) has been associated with elevated levels of Pseudomonadota, which promote mucosal inflammation. These changes can also increase bacterial adherence, penetration into the mucus layer, and migration toward intestinal crypts, amplifying the pro-inflammatory potential and promoting

chronic inflammation. [40] P80 intake may even facilitate the translocation of bacteria, such as Escherichia coli, through M cells and Peyer's patches, thereby compromising intestinal barrier integrity. [41,42]

Xanthan Gum (INS 415), an extracellular polysaccharide from Xanthomonas campestris, is a common food additive. Recent studies suggest that human gut microbiota can partially degrade xanthan gum. [43] Individuals with Westernized gut microbiota often harbor specific bacterial species, particularly from the Ruminococcaceae family, that can metabolize xanthan gum into oligosaccharides, which are subsequently utilized by *Bacteroides intestinalis*, forming a microbial food chain. This degradation can lead to the production of SCFAs, including butyrate, which is known for its anti-inflammatory and gut-protective actions. [43] However, the effects are not uniformly beneficial. Other studies suggest that xanthan gum can induce alterations in the microbiota, promoting the proliferation of opportunistic bacteria, such as *Ruminococcus gnavus* and members of the Enterobacteriaceae family, both of which are associated with intestinal inflammation. [43] For instance, a study in Wistar rats administered xanthan gum found a significant increase in inflammatory cytokines (IL-1β and TNF-α) and harmful modulation of epithelial tight junction proteins, such as Claudin-2, suggesting that at high doses or in predisposed individuals, xanthan gum may compromise intestinal barrier integrity and foster an inflammatory environment. [35,43]

4.2. Non-Caloric Artificial Sweeteners

Non-caloric artificial sweeteners (NAS) are widely used for their calorie-free sweetness and have been implicated in adverse gut health outcomes. Suez et al. [30] observed that NAS intake impairs glucose tolerance in both humans and rodents, with changes directly linked to the gut microbiota, including an overgrowth of *Bacteroides* and a reduction in Bacteroidota, particularly Clostridiales species. Another study linked the consumption of artificial sweeteners, including sucralose, to alterations in gut microbiota and an increased inflammatory potential, suggesting intestinal barrier dysfunction and elevated inflammatory markers such as TNF-α and IL-6. [3]

4.3. Maltodextrin

Maltodextrin, a widely used polysaccharide additive, improves food texture, flavor, and stability. However, frequent consumption may be linked to changes in microbial phenotype and host antibacterial defenses. [44] A study by Laudisi et al. [32] observed that rats given a 5% maltodextrin solution in water for 45 days exhibited a reduction in intestinal mucin 2 (Muc-2) and an increase in epithelial adhesion of pathogenic bacteria, which could contribute to susceptibility to intestinal diseases. [32]

4.4. Carrageenan

Carrageenan (CGN) is a natural polysaccharide extracted from red algae, widely used in the industry for its gelling, thickening, and stabilizing properties. [45] However, its use has been questioned due to its potential breakdown in the gastrointestinal tract, leading to the formation of degraded carrageenans (dCGNs), which may pose health risks. [46] An *in vitro* study by Han et al. observed that the formation of dCGNs by the intestinal microbiota significantly increased the production of nitric oxide (NO2), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines like IL1-b, TNF-a, and IL-6, which suggests a possible link to the development of IBD. [38]

4.5. Synthetic Colorants (Azo Dyes)

Synthetic colorants have experienced a dramatic 500% increase in use over the past five decades, primarily to enhance product appearance. [47,48] These colorants, typically derived from petroleum, release reactive or toxic aromatic amines when metabolized in the gut. These metabolites possess carcinogenic potential and are associated with other chronic diseases. [48,49] Azo dyes (AZo), including Allura Red, Sunset Yellow, Amaranth, Tartrazine, Red 40, and Yellow 6, though permitted

in food, have been linked to microbiota-related disease pathophysiology. [50] The Lachnospiraceae family, including species like *Clostridium symbiosum* and *Hungatella effluvi*, appears to be a primary group capable of reducing AZo dyes. [49] He et al. administered Red 40 and Yellow 6 to genetically susceptible rodents. They found that commensal bacteria like Bacteroides ovatus and Enterococcus faecalis metabolized these dyes to form sodium salt 1-amino-2-naphthol-6-sulfonate (ANSA-Na). [34] This metabolite was then implicated in colitis induction by activating pathogenic CD4+ T cells through the IL-23 axis, stimulating IFN-γ production, and intensifying intestinal inflammation in response to exposure to Red 40 and Yellow 6. [34]

4.6. Nanoparticles and Microparticles

Nanoparticles are increasingly used to enhance product characteristics such as color, texture, and appearance while improving stability and shelf life. [51] An in vitro study evaluating the absorption and biological impact of iron oxide (E172) nanoparticles subtypes (yellow, orange, red, and black) found that all variants interacted with intestinal barrier cells. However, none demonstrated cytotoxic effects at concentrations below 100μg Fe/mL after 24 hours of exposure. [37]

Commonly used microparticles include titanium dioxide (TiO_2 – E171), a whitening agent; aluminum silicate (AlSi – E559), an anti-caking agent; and silicon dioxide (E551). [52] In 2023, the European Food Safety Authority raised concerns about the genotoxic potential of TiO_2. Despite this, its use remains 'authorized pending further review' by Joint FAO/WHO Expert Committee on Food Additives (JECFA). [53] TiO_2 can alter the intestinal environment by reducing the expression of Muc2, a key protein in mucus layer formation, directly affecting goblet cell function, impairing mucus production and compromising intestinal barrier integrity. [33] *In vitro* research indicates that goblet cells efficiently absorb TiO_2, which may interfere with their ability to secrete mucus effectively. [33] Rodent studies show that TiO_2 ingestion leads to its uptake by intestinal cells, initiating a pro-inflammatory cascade. Prolonged exposure has been linked to the release of reactive oxygen species (ROS), resulting in altered gene transcription and promoting dysplasia. [26,52,54,55]

In this context, the harmful effects of UPF components, such as emulsifiers, sweeteners, synthetic colorants, and nanoparticles, are evident through their ability to induce inflammation, alter the gut microbiome, and reduce populations of beneficial microorganisms, thereby possibly contributing to the development of IBD.

5. Dysbiosis and Modulation of the Intestinal Microbiota in IBD

5.1. Microbial Dysbiosis in IBD

IBD is strongly linked to gut dysbiosis, a microbial imbalance characterized by an overgrowth of pathogenic bacteria such as *Clostridium* and *Enterococcus*. [9] This microbial alteration compromises mucosal integrity, increases intestinal permeability and facilitates bacterial translocation, ultimately leading to the intense activation of host inflammatory responses. [56] In individuals with IBD, a significant reduction in the phyla Bacillota (formerly *Firmicutes*) and Bacteroidota (formerly *Bacteroidetes*) is commonly observed. [57] This decrease impairs the modulation of inflammatory responses and the production of SCFAs. Conversely, opportunistic pathogens, including certain Pseudomonadota (formerly Proteobacteria*)* species, proliferate and can exacerbate underlying inflammatory conditions (Figure 2). [58,59] Studies, such as that by Santana et al., [60] confirm that individuals with IBD show a decreased abundance of beneficial bacteria and an increased presence of species that contribute to ongoing mucosal damage (Tables 2 and 3).

Table 2. Main Phyla affected patients with Inflammatory Bowel Disease.

Phylum	Description	Reference
Bacteroidota and Bacillotas	It comprises 90% of the gut microbiota and is often reduced, potentially impairing the inflammatory response and short-chain fatty acid production.	Giambra et al. [57]; Santana et al. [60]
Proteobacteria	It typically increases, including opportunistic pathogens, such as Enterobacteriaceae and Burkholderiaceae, that can exacerbate inflammation.	Alam et al. [58]
Actinobacteria	In patients with Crohn's disease, they are increase, which influences dysbiosis and intestinal inflammation.	Takahashi et al. [59]

Table 3. Altered bacterial profiles in Inflammatory Bowel Disease contribute to inflammation and exacerbation.[60–63].

Increased in IBD		Decrease in IBD	
Phylum	Species	Phylum	Species
Proteobacteria	*E. coli*		
	Campylobacter spp. *H. parainfluenzae* *E. corrodens*	Verrucomicrobia	*A. muciniphila*
Bacteroidota	*B. fragilis*	Bacillota	*F. prausnitzii* *R. albus* *Eubacterium spp*
Bacillota	*R. torques* *Ruminococcus spp.* *C. hathewayi* *C. bolteae* *R. gnavus*		

SCFAs, particularly acetate, propionate, and butyrate, are microbial fermentation products with significant therapeutic relevance for human health. However, their levels are often altered in individuals with IBD. [61] Among these, butyrate is one of the most extensively studied in this population. It is produced by bacteria such as *Roseburia* spp., *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Clostridium leptum* (phylum Bacillota), as well as *Akkermansia muciniphila* (phylum Verrucomicrobia). Butyrate serves as the main energy source for intestinal epithelial cells and supports cell signaling, proliferation, and differentiation. In addition, it has strong anti-inflammatory effects mediated through the activation of G-protein-coupled receptors. [62,63].

SCFAs also play a critical role in modulating immune responses by inhibiting the NF-κB (Fator Nuclear Kappa B) and histone deacetylases, thereby regulating innate and adaptive immunity. [64] These mechanisms support the restoration of tissue damaged by inflammation. [61] In patients with ulcerative colitis treated with infliximab, enzymes involved in butyrate oxidation (excluding SLC16A1) were found to be elevated in those who responded to biological therapy. These findings suggest that mucosal inflammation interferes with butyrate oxidation. [65] Consequently, the results indicate a correlation between inflammation and gene suppression in SCFA absorption and metabolism.

Obesity and diets high in trans and saturated fats, emulsifiers, processed foods, and alcohol contribute to elevated endotoxin levels, oxidative stress, and the expansion of pathogenic bacterial populations while reducing SCFA production. These changes promote inflammation and increase

the risk of other comorbidities, including diabetes, metabolic dysfunction-associated steatohepatitis (MASLD), [66] and various cardiovascular and neurological conditions. [67–69]
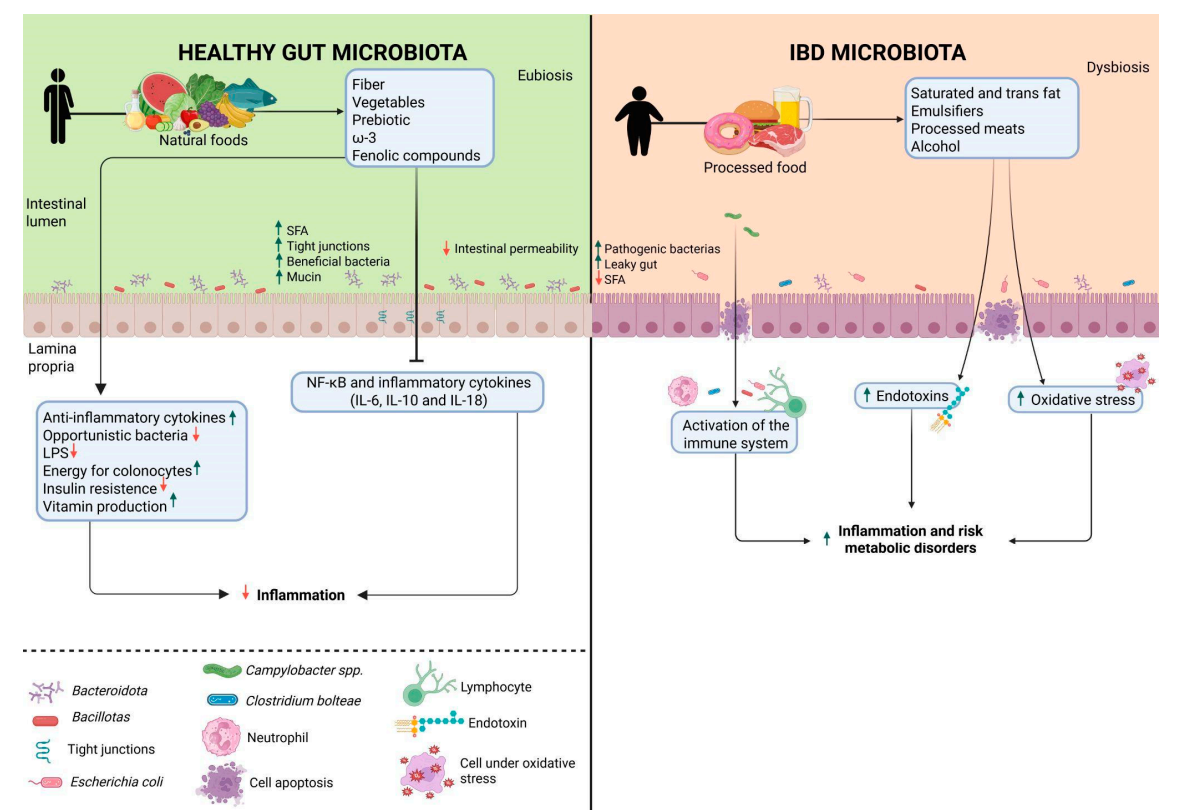

Figure 2. The consumption of whole and/or minimally processed foods is associated with the promotion of an eubiotic environment characterized by increased production of short-chain fatty acids (SCFAs) and mucin, reduced intestinal permeability, lower levels of opportunistic bacteria and inflammatory factors, and elevated anti-inflammatory markers. In contrast, consuming ultra-processed foods contributes to dysbiosis, characterized by an increase in pathogenic bacteria, pro-inflammatory mediators, and metabolic disturbances. LPS: Lipopolysaccharides; NF-kB: Nuclear Factor Kappa B; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-18: Interleukin-18; SFA: Saturated fatty acids; ω-3: omega-3 fatty acids.

5.2. Gut Microbiota Modulation in IBD

Modulating the gut microbiota has emerged as a key strategy in managing IBD[9] and other chronic conditions. [70–72] Various factors, including long-term dietary patterns, physical activity, smoking, sleep quality, alcohol consumption, stress, medication use, and aging, influence the gut microbiota composition. [73] Several approaches are employed to promote intestinal microbiota modulation in individuals with IBD, described below. However, despite promising results *in vitro* and in experimental models, robust clinical evidence supporting their effectiveness in IBD patients remains limited.

5.3. Dietary Patterns

The Mediterranean Diet is a well-researched dietary pattern for its health-promoting effects. [74,75] Rich in fiber, vitamins, minerals, and bioactive compounds, it's associated with a lower risk of IBD development and improved inflammatory markers, alongside a protective effect on the intestinal mucosa. [76,77] Its benefits include reducing pro-inflammatory bacterial species (*Escherichia coli, Ruminococcus gnavus*), increased production of SCFAs, fecal secretory immunoglobulin A (sIgA), and enhanced microbiota diversity and intestinal barrier function. [78–80] Clinical studies support its efficacy. Dogan et al. [81] observed reduced inflammatory biomarkers in UC patients, and Chicco et al. [82] noted clinical

and quality-of-life improvement. Conversely, high consumption of UPF is associated with impaired metabolic and intestinal health, leading to increased inflammation and dysbiosis. [83]

5.4. Prebiotics

Prebiotics are defined as "substrates that are selectively utilized by host microorganisms, providing a health benefit". [84] Examples of such substrates include pectin, inulin, and resistant starch. [85] While the European Society for Clinical Nutrition and Metabolism (ESPEN) suggests potential as an adjunctive therapy in IBD, evidence remains limited. [86] A Cochrane systematic review found insufficient evidence to support their efficacy for induction and maintenance of remission in mild-to-moderate UC, likely due to a few studies. [87]

5.5. Probiotics

Probiotics are live microorganisms that confer health benefits to the host when administered adequately. [84,88] A 2020 Cochrane review analyzing probiotics for maintaining remission in UC found no significant differences compared to other interventions. [89] ESPEN advises against their use for inducing or maintaining remission in CD, as they are generally ineffective. [86] However, probiotics may be considered for mild to moderately active UC and are also recommended for preventing pouchitis. Despite these indications, current evidence does not support their routine use in clinical practice. [90]

5.6. Symbiotic

A symbiotic is defined as a mixture containing live microorganisms and substrates selectively utilized by host microorganisms, offering a health benefit. [91] A meta-analysis suggests that symbiotics may serve as an adjunctive therapy for moderate UC [92] but the limited number of studies necessitates further research. Preclinical studies show promise, but human studies have small sample sizes. [93,94]

5.7. Postbiotics

Postbiotics are preparations of inactivated microorganisms and/or their components confer a health benefit to the host. [95] Studies suggest postbiotics may aid immune modulation via SCFA production, improve intestinal barrier integrity, promote intestinal homeostasis, and inactivate inflammatory pathways. [96] However, most studies with IBD are preclinical or *in vitro*, with heterogeneous outcomes, underscoring the need for more robust clinical trials. [97]

5.8. Fecal Microbiota Transplantation (FMT)

Fecal Microbiota Transplantation (FMT) involves transferring stool from a healthy donor to a recipient's intestinal microbiota. [98] Primarily studied in recurrent *Clostridium difficile* infections and selected metabolic disorders, [97,99–101] a Cochrane review suggests FMT may be a promising therapeutic option for inducing remission in mild-to-moderate active UC. [102] Nevertheless, further clinical trials are essential before FMT can be routinely recommended for treating IBD. [90]

6. The Complex Relationship: UPF, Gut Microbiota, and IBD

The interplay between diet, gut microbiota, and IBD has been a significant research focus in recent decades. [103] Among various dietary factors, UPF has emerged as a critical contributor to gut dysbiosis and the exacerbation of inflammatory conditions, including CD and UC. [103]

Chronic and high intake of UPF is consistently associated with a pro-inflammatory and pro-oxidant metabolic profile [18] mediated through interconnected physiological pathways, including elevated ghrelin levels, reduced peptide YY (PYY) levels, endothelial dysfunction, altered glucose metabolism, hormonal imbalances, and insulin resistance. [104] Furthermore, a higher prevalence of pro-carcinogenic bacteria is observed in the gut microbiota, whose metabolites can induce genotoxic DNA damage. [105] These microbial alterations may also compromise the gut-brain axis, potentially

impairing cognitive function and mental health. [105,106] Elevated UPF consumption, especially in older adults, has been associated with reduced antioxidant enzyme activity (e.g., catalase and superoxide dismutase) and increased levels of xanthine oxidase. [107] These findings indicate increased oxidative stress and diminished antioxidant defenses, accompanied by higher levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-15, and increased production of reactive oxygen species (ROS). [106] The heightened activity of myeloperoxidase (MPO), a pro-oxidant enzyme, further contributes to this pro-oxidative state. [107] These mechanisms may exacerbate endothelial dysfunction, thereby increasing the risk of intestinal ischemia, particularly in vulnerable populations. [104,107] Supporting these observations, a positive association between UPF consumption and IL-6 levels has been found in cohorts from diverse socioeconomic backgrounds. [35] Ultimately, UPF intake significantly influences IBD development and progression by promoting excessive ROS production and perpetuating oxidative stress in intestinal tissues. This oxidative environment directly contributes to cellular dysfunction and can induce necroptosis, thereby amplifying the inflammatory response and exacerbating the clinical course of IBD. [108,109]

Excessive UPF intake is linked to reduced beneficial bacteria, such as *Faecalibacterium prausnitzii*, and decreased production of butyrate, an SCFA essential for maintaining intestinal barrier integrity, as discussed previously. [36,40] A healthy gut microbiota is crucial for immune modulation and intestinal homeostasis, thereby preventing chronic inflammation and protecting against infections. In IBD, this homeostasis is frequently disrupted, leading to dysbiosis marked by reductions in beneficial commensals (e.g., Bacillota and Bacteroidota) and increases in intestinal pathogens (e.g., *Escherichia coli* and Pseudomonadota). [110] A disrupted microbiota in IBD is associated with elevated pro-inflammatory cytokines (including TNF-α and IL-6) and the activation of inflammatory signaling pathways like nuclear factor kappa B (NF-kB), contributing to sustained gastrointestinal inflammation. [110]

External influences, particularly diets high in UPF, exacerbate the pro-inflammatory state, which favors pathogenic bacteria growth and promotes excessive cytokine production. [17] The chronic inflammatory state stemming from UPF intake appears to be a key pathophysiological mechanism contributing to IBD development, particularly in CD. This disruption facilitates bacterial translocation and microbial imbalance, which activate an exaggerated immune response when combined with genetic predisposition, thereby increasing the risk of IBD onset. [26,111–113] (Figure 3).
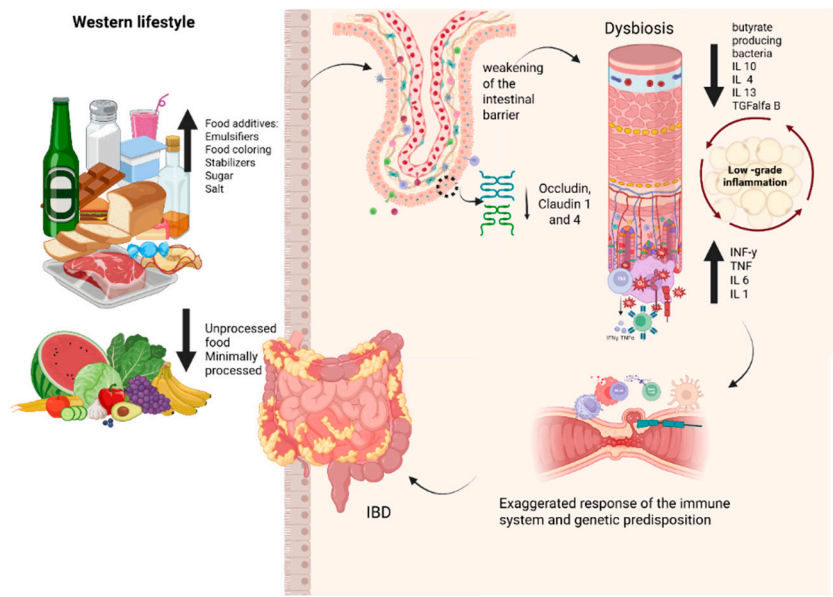

Figure 3. The Western diet's impact on promoting dysbiosis, increasing intestinal permeability, and initiating the inflammatory cascade is a contributing risk factor for developing inflammatory bowel diseases (IBD). IL10: Interleukin-10; IL4: Interleukin-4; IL13: Interleukin-13; TGF-β: Transforming Growth Factor beta; IL6: Interleukin-6; IL1: Interleukin-1; IFN-γ: interferon gama; TNF-α: Fator de Necrose Tumoral alfa.

A robust cohort study involving 245,112 participants in the United States identified 857 IBD cases. [99] High UPF intake was associated with an increased risk of developing CD, linked explicitly to ultra-processed bread, breakfast cereals, and ready-to-heat frozen meals. [99] This association may be attributed to the high levels of carrageenan, synthetic emulsifiers, and sodium chloride in these products, which disrupt the intestinal barrier by promoting the proliferation of pro-inflammatory bacteria within the Pseudomonadota phylum. [99] While this process impairs epithelial integrity and reduces the mucus layer, favoring colitis development, the study found no statistically significant evidence for an association between UPF consumption and UC onset. [99]

Conversely, a 2021 study tracking over 150,000 participants across 31 countries found that higher UPF intake was associated with an increased risk of both CD and UC. However, gut microbiota composition was not assessed. [113] Consumption of UPF, particularly processed meats and soft drinks, was more prevalent in North America, Europe, and South America. [113] However, no food group or additive was independently linked to a higher risk of IBD, emphasizing that overall dietary patterns significantly influence disease pathogenesis. [113] Interestingly, a study in a Caucasian population from eight European countries (over 400 participants, 13.2-year follow-up) found no association between increased UPF consumption and a greater IBD risk. [114] Instead, whole and minimally processed foods appeared to protect against CD, with no significant association for UC incidence. [115]

Beyond incidence rates, research is increasingly focusing on the role of diet in disease progression. [99] Preda et al. (115) conducted a clinical trial of 168 participants with CD/UC. It showed sustained remission in 95.2% of a low-UPF intervention group versus 85.7% in a control group (p = 0.036), after one year, underscoring the role of lifestyle habits in IBD management. [115] Observational studies also suggest an inverse association between high fiber intake and CD risk, though UC results remain inconclusive. [115] Various dietary strategies, such as the CD Exclusion Diet (CDED), have been proposed to support remission in IBD. [115] CDED onsists of structured phases that remove components and additives harmful to the microbiota and intestinal barrier, while emphasizing high-quality proteins and foods that support microbial diversity. This diet is associated with reduced Pseudomonadota and increased Bacilliota. [116] A CDED study showed 76.7% remission by week 6, rising to 82.1% by week 12. [117] In a trial involving children with mild to moderate CD, CDED led to remission, reduced inflammatory markers (C-reactive protein and ESR), fewer bowel movements, and lower fecal calprotectin levels. Participants also reduced their UPF intake and improved their adherence to a Mediterranean diet. [118] The diet's maintenance phase is critical for developing and sustaining healthy eating habits, reinforcing the diet's importance in gut health and microbiome. [119]

7. Final Considerations

Excessive consumption of UPF can lead to various physiological alterations and impair gut microbiota function, contributing to the development of NCDs, including IBD. The impact of UPF on the gut microbiome and its association with the development and progression of IBD is a growing area of research. A high consumption of these foods promotes dysbiosis, increases intestinal permeability, and activates inflammatory pathways, which may exacerbate conditions such as CD and UC. Emerging evidence also supports the link between UPF consumption and increased IBD incidence, particularly CD. Conversely, diets rich in fresh, minimally processed foods promote gut health and may reduce inflammation, improving disease control in individuals with IBD. It is worth noting that few studies have evaluated the effect of UPF consumption on microbiota and the risk of IBD. Most studies have focused specifically on food additives, an area of knowledge essential for informing public policy and guiding regulatory measures. Modulating the gut microbiota through healthy dietary patterns represents a promising approach for preventing and managing IBD in at-risk populations. However, further research is necessary to clarify the underlying mechanisms and determine the most effective dietary interventions. Moreover, nutrition-based strategies aimed at modulating microbiota are expected to play an increasingly vital role in combating chronic diseases,

enhancing patient quality of life, and reducing the broader economic and societal burdens associated with these conditions.

Abbreviations

The following abbreviations are used in this manuscript:

CMC	Carboxymethylcellulose
CD	Crohn's disease
CDED	Crohn's disease Exclusion Diet
IBD	Inflammatory bowel diseases
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-18	Interleukin-18
LPS	Lipopolysaccharides
MASLD	Metabolic dysfunction-associated steatohepatitis
NAS	Non-caloric artificial sweeteners
NCDs	Non-communicable chronic diseases
NF-kB	Fator Nuclear Kappa B
SCFAs	Short-chain fatty acids
SFA	Saturated fatty acids
TIO_2	Titanium dioxide
TLR	Toll-like receptor
TNF-α	Tumor Necrosis Factor
UC	Ulcerative colitis
UPF	Ultra-processed foods

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