Review

Western diet components that increase intestinal permeability with implications on health

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Abstract: Intestinal permeability is a physiological property that allows necessary molecules to enter the organism. This property is regulated by tight junction proteins located between intestinal epithelial cells. However, various factors can increase intestinal permeability (IIP), including diet. Specific components in the Western diet (WD), such as monosaccharides, fat, gluten, salt, alcohol, and additives, can affect the tight junctions between enterocytes, leading to increased permeability. This review explains how these components promote IIP and outlines their potential implications for health. In addition, we describe how a reduction in WD consumption may help improve dietary treatment of diseases associated with IIP. Research has shown that some of these components can cause changes in the gut microbiota, leading to dysbiosis, which can promote greater intestinal permeability and displacement of endotoxins into the bloodstream. These endotoxins include lipopolysaccharides derived from gram-negative bacteria, and their presence has been associated with various diseases, such as autoimmune, neurological, and metabolic diseases like diabetes and cardiovascular disease. Therefore, nutrition professionals should promote the reduction of WD consumption and consider the inclusion of healthy diet components as part of the nutritional treatment for diseases associated with increased intestinal permeability.

Keywords: permeability, western diet, tight junctions, gut microbiota, gut

Introduction

The intestinal barrier can regulate permeability through various components, including the immune system, the enteric nervous system, and intestinal epithelial cells with their respective intercellular junctions and cytoskeletons. Also, the intestinal microbiota plays an important role in intestinal barrier and permeability integrity through the regulation of epithelial repair, metabolism and maintenance, and inflammatory responses [1]. However, this barrier must be permeable for certain substances essential for life.

Intestinal permeability (IP) is the physiological property that allows the selective entry of nutrients, water, and ions for their subsequent arrival in the bloodstream [2]. The molecules passage of the intestinal epithelium occurs through two pathways: the transcellular pathway (via intracelullar) involves the transportation of molecules through intracellular transfer, used by most dietary components like glucose, amino acids, fatty acids, vitamins, and some ions, and the paracellular pathway (via intercellular junctions) as a permeation of hydrophilic molecules, ions and water. These intercellular junctions, made up of a multiprotein complex known as tight junctions (TJs), anchor junctions, and desmosomes, can separate and allow the entry of small molecules [3]. In some cases, nutrients in high concentrations in the lumen can cross the epithelium through this pathway [4]. Nevertheless, the breaking of these protein junctions can lead to an increase in intestinal permeability (IIP).

An IIP implies an abnormal displacement of pathogenic microorganisms, antigens, and toxins [5], generating intestinal deterioration or signs of inflammation and intoxication [4], which could have an important association with some pathologies. For example, recent studies have reported a prevalence of IIP in 30% of people with type 1 diabetes, 34.3% with Crohn's disease, 10.5–42.9% with ulcerative colitis, 34.3% with systemic sclerosis, 35% with cirrhosis, and others [6]. Some of these diseases are related to the presence of variants associated with IIP. For example, the PTGER4 gene variants for Crohn's disease, which is related to an anormal redistribution of TJs and the cytoskeleton [7]. However, 4.6 to 6.8% of healthy people have been shown IIP [6], which can be explained by other causes, not by a specific disease.

Some factors can cause IIP. For example, studies have reported that infections alter IP. *Salmonella* penetrates the tissues and causes a rupture in the TJs [8]. Stress is another

common cause of IIP; it reduces blood flow to the digestive system, increasing the content of toxic metabolites that cause damage to the intestine. Because there is insufficient flow, the intestine cannot be properly repaired, leading to changes in the TJ structure that allow more toxic metabolites to enter the bloodstream, further disrupting the gut-brain connection [9]. Food allergy is associated with a defect in intestinal function. Some food allergens can pass through the intestinal epithelium, activating mast cells that release inflammatory cytokines and proteases that modify TJ proteins. This modification generates greater permeability and passage of food antigens [10].

Finally, it has been reported that some diet components can promote an IIP [11]. This effect is related to certain food components of natural origin (gluten and polyunsaturated fatty acids) and others that are added to food (salt, sugars, and additives). These components are found in a WD, a dietary pattern characterized by "fast food", processed and ultra-processed products high in calories, fat, additives, and sugar but low in vitamins, minerals, and fiber [12].

WD consumption is increasing more and more in several countries and is still prevalent in North America [13] Ultra-processed products, the base of the WD, represent up to 60% of the calories consumed in the USA, increasing consumption in young people, low educational levels, and lower-income strata [14]. Long consumption of WD increases inflammation processes and compromises the immune system at the systemic level, promoting the appearance of certain diseases such as metabolic syndrome, obesity, and diabetes [15]. Also, consuming this dietary pattern promotes "dysbiosis" [16], a term that refers an imbalance in the intestinal microbiota, increasing pathogenic microorganisms and reducing those that can benefit health. A diet high in sugars (sucrose and syrup fructose) and fat, common in the WD, alters the intestinal microbiota [17, 18]. This change in the microbiota can increase toxic metabolites in the intestinal lumen, which can easily cross the intestinal barrier when IIP occurs.

Lipopolysaccharide (LPS), also called endotoxin, is a type of lipid found on the membrane surface of most Gram-negative bacteria and is considered a toxic metabolite. Endotoxemia is generated when LPS crosses the intestinal barrier and circulates in the blood system through LPS-binding protein (LBP). The LPS-LBP complex stimulates cells from the innate immune system, such as monocyte and macrophage, by binding with Toll Like Recetor-4 (TLR4) and cluster of differentiation 14 (CD14), which induce to produce cytokines and promote inflammation [19, 20]. Another metabolite is trimethylamine, a compound generated by bacteria and transformed into Trimethylamine N-oxide (TMAO) in the liver, whose presence in circulation induces systemic inflammation and is considered a cardiovascular risk factor [21].

The toxic metabolites that cross the intestinal barrier could gradually affect the individual's health until it becomes a disease. In addition, prolonged consumption of the WD could contribute to the development of diseases due to the presence of the components in the blood (high concentration of glucose or fat) and the intestinal implications it could cause. Therefore, this review presents an explanation of how consuming WD components can promote the development of IIP. It also provides a schematic representation of the possible process involved and discusses the potential implications of WD consumption on health. Furthermore, the review sheds light on the association or development of certain diseases with IIP. Finally, it emphasizes the importance of reducing WD consumption as a part of an adequate dietary treatment. For the literature search process, various electronic databases were utilized, including MEDLINE, PubMed, Science Direct, Scopus, and Google Scholar. The selection criteria for original articles included experiments conducted on animals or *in vitro*, utilizing molecular techniques such as Western Blot and RT-PCR. Additionally, articles published between 2003 to 2023 articles were selected primarily to ensure the most up-to-date molecular processes were evaluated.

Intestinal barrier

The intestinal barrier is a complex functional unit characterized by an organization in a multilayer system that provides physical and functional protection to the gastrointestinal tract. The intestinal barrier has three main components: lumen, mucosal layer, and intestinal epithelium. The lumen represents the first line of gastrointestinal defense due to the destruction of pathogenic agents and harmful substances by pH, gastric secretions, and microbiota. The mucus layer comprises a layer of water, glycocalyx and glycoproteins, which prevents bacteria's adhesion and secretes peptides such as lysozymes and defensins [1, 2]. The intestinal epithelium contains several types of cells, such as enterocytes found in the small intestine, and colonocytes that are present in the colon. Enterocytes and colonocytes are responsible for absorbing nutrients and water. Additionally, there are enteroendocrine cells that secrete hormones, goblet cells that are responsible for producing mucin, and paneth cells that release antimicrobial peptides [22].

Intercellular junctions

Intercellular junctions are essential in intestinal homeostasis, allowing the intestinal tissue's epithelial cells to remain connected. These junctions can be divided into tight junctions (TJ), anchor junctions, and desmosomes (Figure 1).

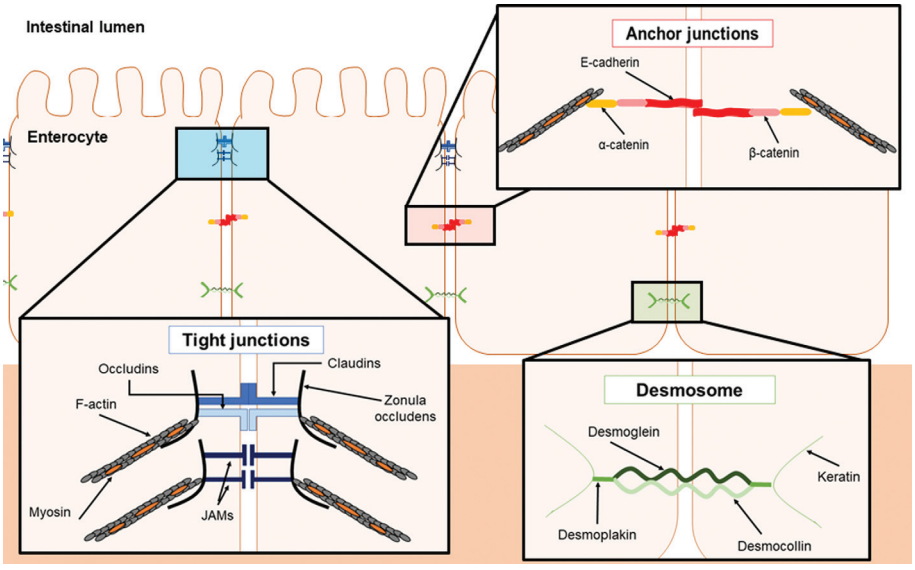

Figure 1. Graphic representation of the intercellular junctions of the intestinal epithelium. Tight junctions control the passage of nutrients, while anchor junctions and desmosomes allow cell adhesion and communication. *Abbreviation:* JAMs: junctional adhesion molecules.

TJ are multiprotein complexes that form semi-permeable connections between epithelial cells, capable of regulating the paracellular entry of nutrients, ions, and water. This multiprotein complex is made up of different transmembrane proteins, such as occludin, claudins, and junctional adhesion molecules (JAMs), which interact with peripheral proteins called zonula occludens (ZO) (Figure 1) [23].

Occludin fulfills TJ's assembly and disjunction functions, while its phosphorylated segments' interaction with ZO allows paracellular permeability regulation. In addition, it also plays a significant role in regulating oxidative stress at the intestinal cells [24, 25]. Furthermore, claudins regulate the paracellular movement of ions since some amino acids in their structure alter ion selectivity, giving them similar characteristics to ion channels [26]. Furthermore, JAMs are involved in the contact between intestinal cells, the processes of formation and assembly of the TJ, and the anchoring unions [27]. Finally, ZO are linked to the transmembrane proteins of the TJ and the cytoskeleton's actin filaments (F-actin). These interactions facilitate cell proliferation, differentiation and signaling, and strengthening of the TJ [28].

Anchorage junctions provide structural resistance to intestinal epithelial cells by adhering their respective actin cytoskeletons to each other. The interactions between the cytoskeletons of these cells are possible thanks to proteins such as E-cadherin, α-catenin, and ß-catenin. In conjunction with desmosomes, anchor junctions allow communication between adjacent cells. Desmosomes are protein complexes that connect the walls of neighboring cells in multiple regions to provide resistance and mechanical stability to intestinal cells [29].

Mucin, a glycoprotein secreted by goblet cells and Paneth cells, is another essential element in regulating IP and the integrity of the intestinal barrier. It is the main and priority component of the mucus layer, mucin 2 (MUC2) being the most predominant [30]. As previously mentioned, IP can be altered by components found in the diet. In the following sections, the mechanisms of action of some components that, based on the evidence, are associated with an IIP will be described.

Glucose

The absorption of this monosaccharide occurs through the sodium-glucose linked cotransporter 1 (SGLT-1) in the intestinal epithelium, as well as through the transport protein GLUT-2 in the apical membranes [31], or through the paracellular pathway between TJ of intestinal epithelium cells if there are high concentrations of glucose in the intestinal lumen and a sufficient osmotic gradient to promote volume flow [32].

Hyperglycemia is a principal factor in IIP, and the integrity of the intestinal barrier is disrupted since high serum glucose levels cause a rupture in the TJ between enterocytes (Figure 2A). The mechanism by which IIP is related to high glucose intake is through two mechanisms: 1) retrograde transport of glucose into the enterocyte and 2) paracellular passage of high concentrations of glucose and modification of the actomyosin filaments. The first mechanism, hyperglycemia causes glucose to undergo retrograde transport to intestinal epithelial cells via GLUT-2. In mice, it has been reported that hyperglycemia causes retrograde

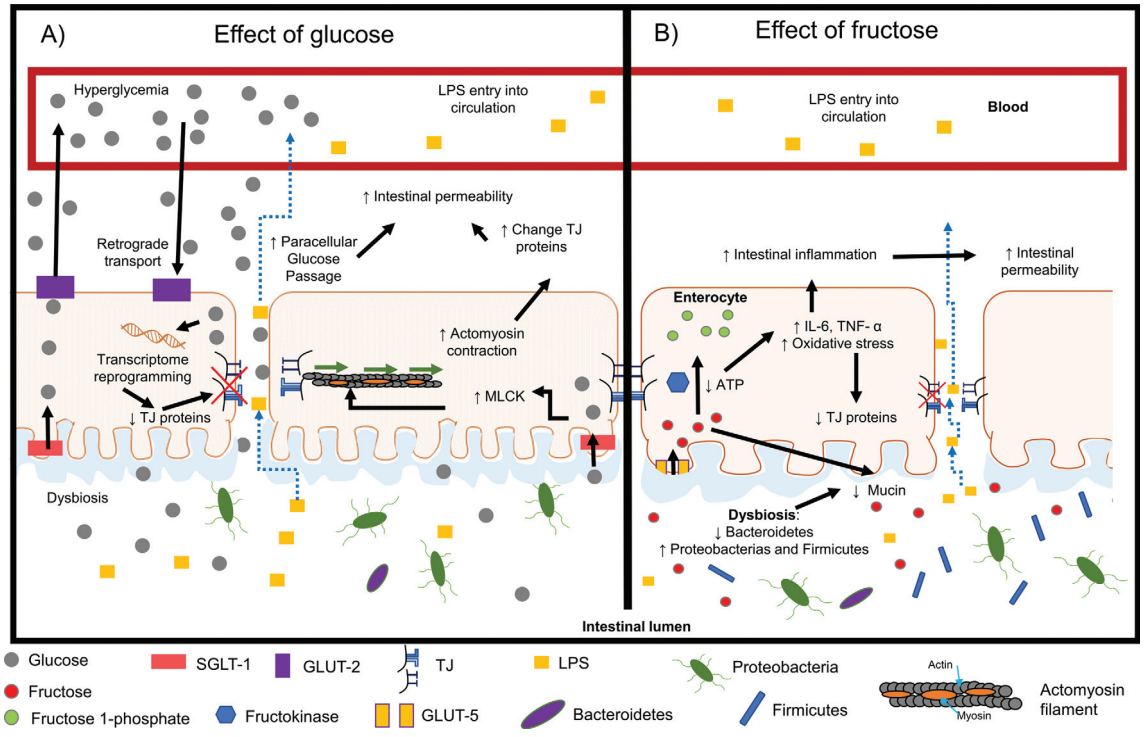

Figure 2. Effect of glucose and fructose on intestinal permeability. (A) The presence of glucose and its paracellular intestinal absorption produces the breakdown and rearrangement of the constituent proteins of the tight junctions (TJ) by transcriptome reprogramming, thus leading to increased intestinal permeability. Likewise, the high amount of glucose can promote the generation of dysbiosis, which is why the passage of endotoxins through the opening between the epithelial cells will be more likely. (B) The metabolic alteration of fructose triggers the inflammatory response, oxidative stress, and dysbiosis, causing a decrease in mucin and TJs proteins, leading to an increase in intestinal permeability. *Abbreviation:* GLUT: glucose transporter; LPS: Lipopolysaccharides; MLCK: myosin light chain kinase; SGLT-1: sodium-glucose linked transporter-1.

transport into the enterocytes through GLUT-2 and reprogramming in the epithelial transcriptome, with a decrease in the expression of genes involved in the glycosylation of proteins responsible for cell stability, including TJ proteins [33]. The second mechanism, high glucose concentration in the intestinal lumen can pass between the junctions of the enterocytes, generating a rupture between TJs proteins. Research with Caco-2 cells has reported that an increased glucose flux by SGLT-1 stimulation causes the activation of myosin light chain kinase (MLCK), which phosphorylates a portion of myosin, and consequently, it induces the contraction of the filaments of the actomyosin cytoskeleton and the rearrangement of the TJ proteins, causing the increase on paracellular permeability [23, 34].

A high-glucose diet may promote the development of intestinal microbiota dysbiosis. Studies in mice have reported an increase in the proportion of *Proteobacteria* and a decrease in *Bacteroidetes* after consumption of a high-glucose diet. Additionally, an IIP associated with decreased levels of ZO and occludin was found in these studies. However, the exact mechanisms are unknown, but intestinal dysbiosis may play an important role [35, 36]. These modifications in the gut microbiota promote the presence of gram-negative bacteria and increased levels of LPS in the blood, increasing the risk of endotoxemia. The control of hyperglycemia is thought to restore intestinal barrier integrity [37]. It has been reported that insulin administration can reverse the effects caused by hyperglycemia in the intestinal barrier and IP integrity [33]. Also, it has been shown that the use of anti-hyperglycemic agents such as metformin and peroxisome proliferators activated receptor-γ (PPAR-γ) agonists can alleviate intestinal barrier injuries and improve intestinal barrier function [38, 39].

Fructose

This carbohydrate can be found naturally in fruits, vegetables, and honey or added to food products such as drinks and nectars. However, in recent times the consumption of fructose has increased, especially as a caloric sweetener in the form of high fructose corn syrup (HFCS), a mixture of glucose and fructose used in baked goods, tomato-based sauced, jams, carbonated drinks, and junk food [40].

Fructose is absorbed through the GLUT-5 transport protein located in the apical membrane of enterocytes and is transported into the systemic circulation through the basolateral GLUT-2 transport protein to reach the liver [41]. Fructose can be metabolized in the liver and intestine by

the fructokinase (ketohexokinase) enzyme to generate fructose-1-phosphate using adenosine triphosphate (ATP) molecules. This fructose conversion allows glucose synthesis [42].

The alteration of intestinal metabolism of fructose can lead to IIP (Figure 2B). The fructokinase enzyme does not have retroinhibition control, so there is no way it can stop its activity. This reaction requires a large amount of ATP, causing a reduction of this nucleotide, which stimulates adenosine deaminase activity, leading to a degradation of adenine nucleotides to produce intracellular uric acid, a molecule capable of producing oxidative stress [43, 44]. An increase in intestinal fructokinase expression in mice was found, along with a reduction in the expression of TJ proteins, which caused IIP [42].

Furthermore, excessive fructose consumption has been related to proinflammatory responses in the liver and intestine [45]. The fructose-induced inflammation in mice, increased expression of TLR4 and Myeloid differentiation primary response 88 (MyD88), important participants in chronic inflammation [46, 47]. Also, the high intake of fructose in mice has been associated with high levels of plasma proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) along with a decrease in the expression of ZO-1 and occludin, leading to the IIP [48].

Other studies have reported a high-fructose diet-induced gut dysbiosis in mice with a significantly increased abundance of *Proteobacteria* and *Firmicutes* and decreased abundance of *Bacteroidetes*. A decrease in the expression of occludin and ZO-1 and an increase in serum endotoxin levels were also reported in these studies [36, 49]. In rats, the dysbiosis caused by diets enriched in fructose increased the predominance of mucin-degrading bacteria, causing a reduction in the mucin glycoprotein on the intestinal mucus and destabilization of intestinal barrier integrity [50].

High-fat diet

According to the literature, a high-fat diet is directly associated with alterations of intestinal barrier integrity by developing the appearance of IIP [51]. This phenomenon can be caused by two mechanisms: the development of intestinal dysbiosis and the alteration in intestinal absorption and metabolism of lipids (Figure 3A) [51, 52].

As mentioned, the consumption of high-fat diets could generate gut dysbiosis. Numerous studies in rodent models have demonstrated that a high intake of dietary fat can reduce amount of of *Lactobacillus*, *Bifidobacterium*, *Bacteroidetes*, and *Akkermansia* and increase *Oscillibacter* and *Desulfovibrio* [53, 54, 55, 56, 57]. The increase of *Desulfovibrio* bacteria, specifically *Bilophia wadsworthia*, is also stimulated by colonic levels of bile acids, such as taurocholic acid. In rats, it was demonstrated that *Bilophia wadsworthia* produces hydrogen sulfide (H_2S), which can inhibit the oxidation of short-chain fatty acids, such as butyric acid, causing an energetic imbalance in enterocytes leading to possible cell hypoplasia and IIP [53].

Gut dysbiosis is accompanied by an excessive luminal content of LPS derived from gram-negative bacteria membranes. Studies in Caco-2 cells have probed that LPS can interact with the LBP in enterocytes or CD4 immunological cells [58]. This interaction causes the activation of TLR4 and stimulates NF-kb activity, inducing an increased expression and release of proinflammatory cytokines such as IL-6 and TNF-α and oxidative agents such as nitric oxide. This inflammatory process and oxidative stress influence the regulation of TJ proteins synthesis and IIP [59, 60].

The intestinal barrier can resist the solubilizing of bile acids; however, a high intake of fat could cause an uncontrolled presence of deoxycholic acid and chenodeoxycholic acid in the intestinal lumen, promoting the alteration of TJ proteins and lead to an IIP [61]. A study with Caco-2 cells has demonstrated that deoxycholic acid and chenodeoxycholic acid stimulates the epidermal growth factor receptor (EGFR). This mechanism causes the activation of SRC kinase and subsequent serine-threonine dephosphorylation of the occludin tail, which causes the separation between occludin and ZO-1, leading to the IIP [62].

Furthermore, a high-fat diet consumption increases the damage susceptibility of intestinal mucosa due to an accumulation of chylomicrons in the intercellular spaces between enterocytes. This accumulation causes an increase in local pressure and loosening of TJ proteins, in addition to the appearance of perforations on the basolateral membranes of the enterocytes, promoting the possible IIP [63]. In addition, LPS can be incorporated into chylomicrons via its lipid tail, promoting the development of endotoxemia due to a high amount of LPS in the blood in IIP conditions [64].

ω-6 fatty acids

Polyunsaturated fatty acids contain more than one double bond in their chemical structure. The ω-6 fatty acids are characterized by inducing proinflammatory responses by having a high susceptibility to oxidation and competing with ω-3 fatty acids in elongation and desaturation reactions [65].

Arachidonic acid (AA) is the most known ω-6 fatty acid, thanks to its relation to the inflammatory cascade, as it is its main precursor. AA can be obtained in two ways: through the elongation of linoleic acid or the consumption of foods of animal origin, such as eggs, poultry, organ meats, and fish. After its release in response to injury, AA can be

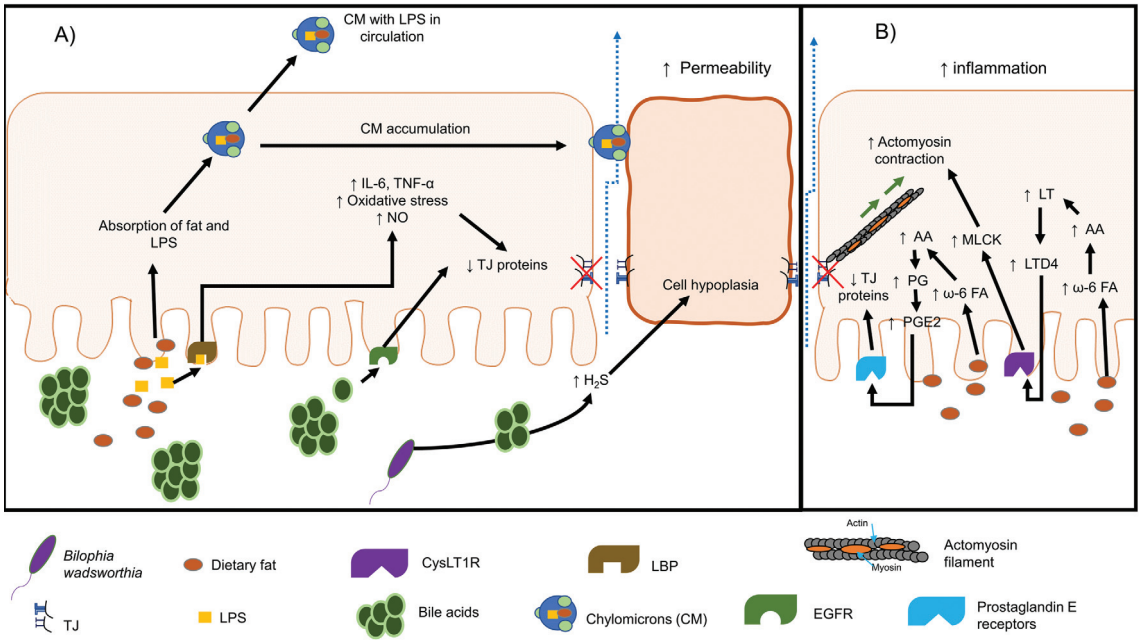

Figure 3. Effect of fat on intestinal permeability. (A) A high-fat diet promotes dysbiosis in the intestinal lumen, interacting with the bile acids that promote cell apoptosis and activate inflammatory and oxidation processes. In addition, increased fat absorption promotes increased chylomicron (CM) synthesis, which tends to accumulate between tight junctions (TJ) and promotes increased intestinal permeability. (B) A high consumption of ω-6 fatty acids (FA) causes a decrease in TJ proteins, contraction of the actomyosin complex, and the promotion of inflammation processes. *Abbreviations:* AA: Arachidonic acid; CysLT1R: Cysteinyl leukotriene; receptor 1 EGFR: epidermal growth factor receptor; IL-6: Interleukin-6; LBP: lipopolysaccharide binding protein; LPS: Lipopolysaccharides; LT: Leukotrienes; LTD4: Leukotriene D4; MLCK: myosin light chain kinase; NO: nitric oxide; PG: prostaglandins; TNF-α: Tumor Necrosis Factor-α.

metabolized into lipid substances called eicosanoids through four pathways: cyclooxygenase (COX), lipoxygenase (LOX), cytochrome P450, and reactions triggered by reactive oxygen species. These pathways create different lipid mediators, such as prostaglandins (PG), leukotrienes (LT), lipoxins (LX), and thromboxanes (TX), which act in the inflammatory cascade [66].

Regarding the intestinal barrier and IP, AA represents the most studied ω-6 fatty acid (Figure 3B). Intestinal epithelial cells can metabolize AA into eicosanoids such as PG and LT. Research with Caco-2 cells has shown that an increase in LT, especially LTB4, and LTD4, causes a decrease in the presence of TJ proteins. LTD4 binds to the cysteinyl leukotriene receptor 1 (CysLT1R) and causes the activation of MLCK. This activation can lead to the contraction of the actomyosin filaments and the redistribution of occludin. This mechanism can increase paracellular permeability [67]. In addition, studies with Caco-2 cells probed that PGE2, a COX inflammatory metabolite derived from AA, increases paracellular permeability due to its interaction with prostaglandin E1 and E4 receptors. This interaction causes a redistribution of TJ proteins like occludin and claudin [68, 69]. Currently, the consumption of ω-6 fatty acids is high and is commonly found in processed products. Therefore, high consumption of this type of fat and products could influence the generation of an IIP.

Gluten

Gluten is a complex of glycoproteins found abundantly in cereals and grains such as wheat, rye, barley, and oats, the latter due to contamination by wheat gluten during processing. Gliadin is the most important protein in gluten, which is antigenic and predisposes to developing celiac disease or non-celiac gluten sensitivity in susceptible individuals. This susceptibility is due to the proteases deficiency in the human intestine and the rich content of glutamine and proline residues in the composition of gliadin. The deficiency of proteases causes incorrect protein hydrolysis, so gliadin peptide segments are generated. These peptide segments can cause damage to the homeostasis of the intestinal barrier [70, 71].

The IIP caused by gliadin occurs through zonulin, a paracrine protein that can modulate IP (Figure 4) [72]. Studies in mice have reported that zonulin is released from the intestinal epithelial cells to the intestinal lumen through the interaction of gliadin with the chemokine receptor CXCR3 due to a MyD88 protein-dependent pathway [73]. After reaching the lumen, zonulin binds with EGFR located in the enterocyte membrane with the help of protease-activated receptor 2 (PAR2). This mechanism was demonstrated in both Caco-2 cells and mice [74]. The interaction between zonulin and EGFR stimulates protein kinase C-α,

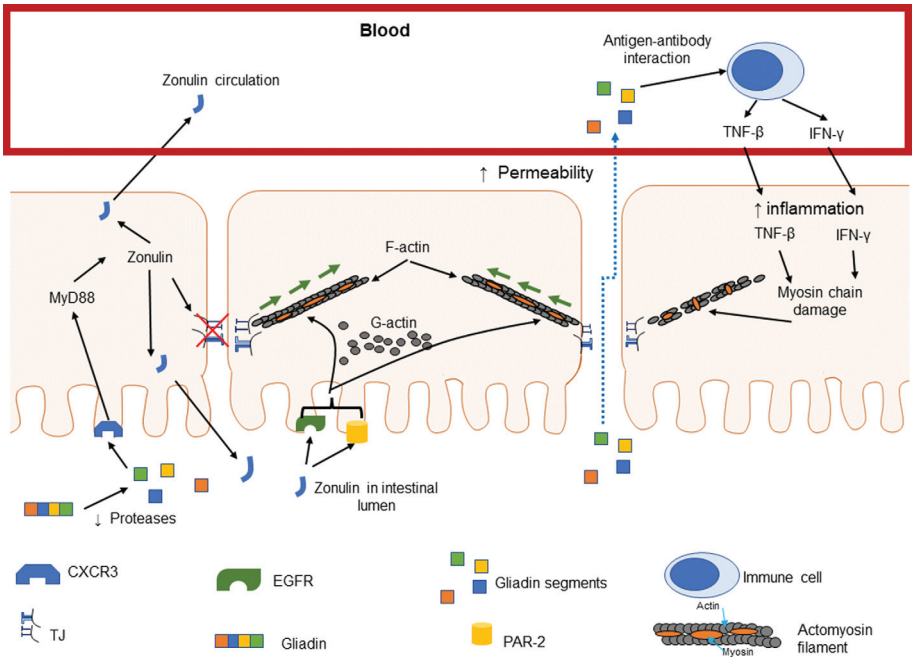

Figure 4. Effect of gluten on intestinal permeability. The segments of the gliadin constituent of gluten achieve the release of zonulin, triggering the displacement of the tight junctions (TJs) proteins and favoring the increase in intestinal permeability. This action leads to the gliadin segments passing paracellularly and promoting the activation of the immune system, causing greater inflammation in the cells. *Abbreviations:* CXCR3: chemokine receptor-3; EGFR: epidermal growth factor receptor; IFN-γ: interferon-γ; MyD88: myeloid differentiation primary response 88; PAR-2: receptor activator of proteinase-2; TNF-ß: tumor necrosis factor-ß.

transforming G-actin into F-actin through a polymerization process, leading to the reorganization of the enterocyte cytoskeleton and TJ proteins such as ZO-1 and occludin, promoting the development of IIP [72, 75]. This reorganization allows an excessive entry of antigens (in this case, gliadin fragments), and their subsequent interaction with immune cells promotes the synthesis and release of proinflammatory cytokines such as tumor necrosis factor-beta (TNF-ß) and interferon-gamma (IFN-γ), which causes the disassemble of TJ and the IIP [76].

IIP and high serum levels of zonulin have been found in patients with celiac disease [77] and Crohn's disease, along with overexpression of chemokine receptor CXCR3 [78]. If gluten is removed from the diet, the serum levels of zonulin may decrease, and the IP may stabilize [79]. However, the presence of gluten does not necessarily determine that there may be damage to IP in the general population. Gluten susceptibility only appears when protein digestibility is incorrect due to decreased proteases in the intestine, generating gliadin fragments that can interact with CXRC3 receptors and induce the cascade of reactions.

High-salt diet

Adherence to high-salt diets (especially in sodium chloride) represents an important etiological factor in the risk of developing proinflammatory processes and intestinal problems [80]. Unfortunately, there is not enough research on the effects of salt on IP. However, there is evidence that increased salt intake can generate dysbiosis and alter intestinal epithelial cells (Figure 5).

The intestinal microbiota can be affected by a high-salt diet; for example, studies in mice models have reported that an increased intake of salt is related to an increased abundance of *Parasutterella, Erwinia, Ruminococcus,* and *Lachnospiraceae* [80, 81, 82, 83] and a decreased abundance of *Lactobacillus, Oscillibacter, Pseudoflavonifractor, Johnsonella,* and *Rothia* [80, 82, 83]. These changes in intestinal microbiota composition promote alterations of microbiota functions. A study in mice has shown that a high-salt diet can impact on proteins and polysaccharides, degrading enzymes secreted by gut microbiota [84]. In association with the intestinal epithelium, high concentrations of sodium can affect cell proliferation due to the formation of cellular hyperplasia along with an early apoptosis induction and the development of cells with altered physiology [85]. Salt stimulates the SGLT-1 transporter and activates sodium-hydrogen exchanger 3 (NHE3), an important absorption pathway for sodium in the small intestine. In cultured cell models, it was demonstrated that the NHE3 stimulation by sodium causes the phosphorylation of the myosin light chain, which promotes the contraction of the actomyosin ring, and, thus, the appearance of IIP [86].

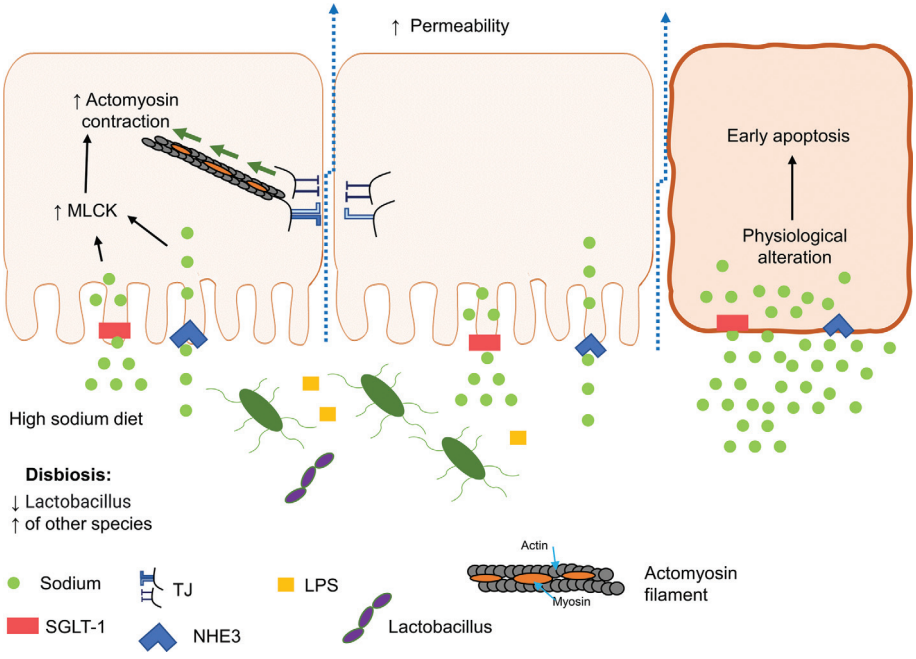

Figure 5. Effect of salt on intestinal permeability. Increased sodium absorption produces alterations in the tight junctions (TJs) and the contraction of the actomyosin filament, promoting increased intestinal permeability. Likewise, high concentrations of sodium induce dysbiosis, mainly the reduction of lactobacillus, which can increase other Lipopolysaccharides (LPS)-generating species and thus aggravate the IP state. Also, the increased absorption of sodium promotes physiological changes in intestinal cells by promoting apoptosis. *Abbreviations:* NHE3: sodium-proton-exchanger subtype 3; MLCK: myosin light chain kinase; SGLT-1: sodium-glucose linked transporter-1.

Alcohol

After oral intake, ethanol is absorbed in the small intestine, specifically in the duodenum and jejunum, thanks to the abundant microvilli in intestinal cells. About 98% of the absorbed ethanol reaches the liver to undergo biotransformation, while the remaining 2% is eliminated through respiration, urine, or enterohepatic circulation [87]. However, it has been observed that high intakes of alcohol can cause an intestinal accumulation of alcohol metabolites, such as acetaldehyde [88].

Alcohol can generate IIP due to the accumulation of acetaldehyde in the enterocytes, which promotes cell damage (Figure 6). Studies in mice and Caco-2 cells have demonstrated that high alcohol exposure significantly reduces TJ proteins [89, 90]. Furthermore, the presence of acetaldehyde in cell culture monolayers caused oxidative stress and the disassembly of the TJ proteins because of a decrease in intracellular zinc levels [80, 90]. In mice, excessive alcohol intake caused alterations in the expression of MUC-2, leading to a partial reduction of the mucus layer on the intestinal barrier [91]. Other studies in mice have shown that chronic alcohol consumption causes intestinal cell loss due to damage to intestinal stem cells [92].

Excessive consumption of alcohol can change the composition of gut microbiota. Studies in alcoholic individuals and patients with alcoholic liver cirrhosis have shown an increased prevalence of *Proteobacteria, Enterobacteriaceae,* and *Streptococcaceae* and a decreased prevalence of *Clostridia, Bacteroidetes, Lactobacillus*, and *Faecalibacterium* [93, 94, 95]. The IIP caused by alcohol has been related to bacterial translocation and the development of endotoxemia, as it occurs together with dysbiosis. In addition, the combination of dysbiosis and IIP is important in the development of diseases and issues in the liver [96, 97].

Food additives

Different international authorities regulate the application of food additives in food products to avoid microbiological and toxic risks to consumers. Despite this, it has been found that some additives can impair intestinal barrier integrity and promote an increase in IP [98, 99].

Synthetic emulsifiers such as carboxymethyl cellulose (CMC) and polysorbate 80 (P80) are added to processed foods to extend shelf-life and improve texture properties. However, these food additives can alter intestinal barrier integrity and promote the appearance of IIP [100]. Studies in mice models have shown that an excessive intake of CMC and P80 causes IIP due to damage in the TJ proteins, decreased MUC-2 synthesis, the development of bacterial translocation, and the appearance of proinflammatory processes [101, 102, 103].

Artificial sweeteners such as saccharin, acesulfame potassium, and saccharin provide sweetness to food and

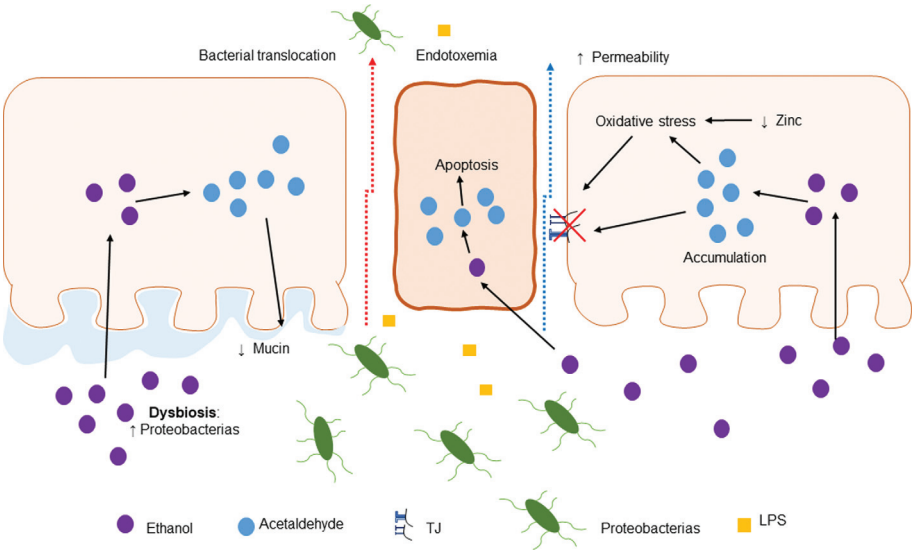

Figure 6. Effect of alcohol on intestinal permeability. Acetaldehyde induces oxidative stress and decreases the presence of tight junctions (TJ) proteins. It can also induce cell apoptosis by its accumulation inside the cell. In addition, ethanol generates dysbiosis in the intestinal lumen, thus increasing the presence of endotoxins and pathogenic bacteria. Combining IP and dysbiosis promotes the risk of endotoxemia and bacterial translocation. *Abbreviation:* LPS: lipopolysaccharides.

beverages [99]. This type of sweeteners has been associated with negative effects on the intestinal barrier. IIP was found in a mice model after high consumption of acesulfame potassium due to excessive proinflammatory cytokines and a reduced expression of glucagon-like peptide (GLP) receptors. These receptors help reinforce TJ protein stability [104]. Another study in rats demonstrated that excessive sucralose intake caused IIP alongside the aggravation of intestinal inflammation and inactivation of digestive proteases [105]. A study with Caco-2 cells demonstrated that saccharine caused IIP due to a reduction of claudin-1 levels [106].

High intakes of synthetic emulsifiers and artificial sweeteners may cause intestinal microbial changes, leading to gut dysbiosis. In mice, high intakes of CMC and P80 decreased the prevalence of *Clostridiales* and *Lactobacillus* and increased the prevalence of *Bacteroidales, Bacteroidetes, Proteobacteria, Helicobactraceae* and *Campylobacterales* [103, 107]. In mice, the consumption of sucralose, acesulfame potassium, and saccharine reduced the amount of *Lactobacillus, Clostridium, Lachnospiraceae, Ruminococcaceae, Roseburia,* and *Turicibacter*. Also increased the amount of *Bacteroides, Sutturella, Proteobacteria, E. coli,* and *Shigella* [108, 109, 110].

The studies have shown that WD components promote IIP, and although these components have been evaluated *in vivo* and *in animals*, their effect on TJ in humans has been proposed as the possible cause of IIP and serum endotoxins. For instance, Molina-Vega et al. [111] reported the presence of serum endotoxins (LPS and LBP) and an increase in IIP markers (zonulin) in obese people after a high-fat load. This suggests that the presence of a high-fat load influences the alterations in TJ. Additionally, it has been demonstrated that a fructose-rich diet elevates bacterial endotoxin plasma levels in healthy people, showing that high-fructose consumption also influences IIP [112]. Astudillo-López et al. [113] evaluated the diet and the presence of IIP markers in young people, revealing an association between high energy, fat, and carbohydrate consumption with high serum concentrations of zonulin and LPS. Although these studies suggest the impact of the type of diet on IIP in humans, further research is required to evaluate the effect of WD components together rather than separately, as most studies have shown.

Health implications of WD and IIP

Overconsumption of the WD has been associated with the development of obesity, metabolic syndrome, and type 2 diabetes, as we mentioned [2, 15]. These diseases are promoted by the hyperglycemia, hyperinsulinism, and a systemic pro-inflammatory process due to the high-sugars and high-fat consumption from ultra-processed products [104, 114].

It is evident that the WD components can contribute to the development of certain diseases. However, they also affect IIP and development of dysbiosis due to their presence in the intestinal lumen. An IIP allows the passage of metabolic products and antigens caused by dysbiosis. Once they enter the circulatory system, they can significantly alter the immune system, leading to an inflammatory process. Therefore, metabolites such as LPS may cause or

contribute to the development of certain diseases. For instance, studies have shown that IIP exists in patients suffering from autoimmune, neuroinflammatory, and metabolic diseases [115].

An immune system overstimulated can promote the development of autoimmune diseases, which generate antibodies against the organism's antigens, causing the immune system to attack tissues. The causes of autoimmune disease can be environmental, physiological, or genetic factors. However, the presence of IIP could influence the development of the disease. IIP has been reported in type 1 diabetes mellitus (T1DM), ankylosing spondylitis, celiac disease, systemic lupus erythematosus (SLE), multiple sclerosis, and others [116, 117, 118, 119, 120].

In T1DM, it has been reported that IIP can start before disease onset [121]. Children with IIP showed multiple higher islet autoantibodies and progressed to DM1, evaluating it by the blood lactulose:rhamnose ratio, compared to those who did not progress [116]. Furthermore, higher serum levels of LPS and zonulin have been observed in patients with T1DM [122, 123].

Recently, a study has reported that a dysbiosis with IIP contributes to the pathogenesis of SLE; there were higher levels of zolunine, soluble CD14 and TRL4 in serum and decreased α-diversity of the intestinal microbiota in patients with SLE than in healthy controls [124]. In addition, differences in the abundance of bacteria and high serum LPS have been reported in patients with SLE compared to healthy people [125]. *Enterococcus gallinarum*, a bacterium that is often present in the liver or blood of some SLE-susceptible patients, has been suggested as a candidate for a "pathobiont", a microorganism that could influence the clinical characteristics of SLE patients [126]. Therefore, IIP and dysbiosis in these autoimmune diseases are common. If autoimmune patients consume a WD, the components could develop dysbiosis, increase intestinal damage, intensify IIP, and generate greater immune system stimulation by allowing the entry of endotoxins. The consequence of overstimulation could make medical treatment fail, such as glucocorticoids and immunosuppressants, the most common treatments used [127].

Neuroinflammatory diseases, such as autism, Alzheimer's disease, major depressive disorders, and schizophrenia have been related to IIP [128, 129, 130, 131]. Neuropathological diseases are related to inflammatory processes in the brain and intestine with the gut-brain axis connection. The presence of dysbiosis and intestine inflammation allow the entry of LPS and bacterial translocation, generating a greater stimulus in the immune system that elevates proinflammatory cytokines. This condition causes the nervous system to be more affected, creating a vicious circle. Increasing the secretion of cortisol will generate an IIP and, with it, an increase in the entry of endotoxins [132].

In autism has been reported a higher zonulin levels than healthy controls, and a correlation between zonulin levels and "Childhood Autism Rating Scale score" [133]. Intestinal fatty acid binding protein (I-FABP) is another IIP biomarker, a cytosolic protein presented in blood when the intestinal epithelium is damaged. It has been shown that increases in serum I-FABP correlate with more maladaptive behavior, communication, and social interaction problems [134]. The inflammation process from IIP and dysbiosis causes Alzheimer's disease to progress more quickly. Dysbiosis and IIP could induce systemic and neuroinflammation with an amyloid-beta (Aβ) peptide aggregation [135]. In the other hand, the bacterial amyloid is a metabolite of the intestinal microbiota that crosses after the IIP and is considered an initiating factor for Aβ aggregation [136]. For example, in experimental studies with *Pseudomona aeruginosa*, a bacterium that colonizes intestinal infection, secretes bacterial amyloid peptides that induce Aβ aggregation [137]. Furthermore, elderly patients with brain amyloidosis were shown to have a greater abundance of intestinal *Escherichia/Shigella* and serum proinflammatory cytokines compared to those without brain amyloidosis [138]. Likewise, *Escherichia coli* has been demonstrated to generate amyloid biogenesis [139]. Therefore, we must consider that the development of Alzheimer's can be promoted by an inadequate intestinal barrier, dysbiosis, and the passage of bacterial molecules, although this requires a greater number of studies in patients with this condition. Some psychiatric diseases also are associated with IIP. For example, a study who analyzed IIP biomarkers in patients with schizophrenia have more elevated serum concentration of LBP and zonulin than healthy controls [131]. Likewise, it has been reported dysbiosis in elderly patients with schizophrenia; *Prevotella* in the intestine increased with a positive correlation with proinflammatory cytokines. The authors mentioned that this correlation could be related to the pathogenesis of schizophrenia [140]. As we mentioned, the WD has been associated with the progression of neuroinflammatory diseases. Studies report the relationship of diet with neurological diseases through the microbiota and IIP [141, 142], but not through the direct effect of the components on the neurological system. As a result, consuming the WD should be limited in patients with neurological disease to reduce the IIP, dysbiosis, and neurological damage process.

Finally, metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver have been associated with IIP. Metabolic diseases are related to dietary factors, so part of this review has shown that certain components of the WD are found in high-calories and high-fat foods. In addition, the passage of bacteria and LPS into the circulatory system has been observed to affect normal glucose function, leading to reduced insulin sensitivity through an immune response. Therefore, impaired insulin

sensitivity may promote some of the known metabolic diseases [143].

The presence of dysbiosis and IIP in obesity and DM2 is strongly established, as is the association of both diseases with a high WD consumption [144, 145]. Recently, the term "metabolic endotoxemia" is derived from dietary high-fat consumption and dysbiosis in obese patients, which increases IP and causes a large amount of LPS to pass through the intestinal epithelium. This metabolic endotoxemia induces oxidative stress and inflammation, as a result, influences the development of metabolic syndrome, cardiovascular diseases, and DM2 [146]. For example, a meta-analysis of completed cohort studies examined the relationship of endotoxemia in patients with metabolic syndrome (n=7178). The analysis showed a direct association between LPS concentrations and lipoprotein concentrations such as VLDL, IDL, LDL, small HDL, and serum glucose, among other indicators [147]. Likewise, the presence of endotoxemia is a risk factor for the prevalence and incidence of T2DM, independent of other risk factors such as Body Mass Index (BMI), blood glucose or C-reactive protein [148].

Non-alcoholic fatty liver disease (NAFLD) has been associated with IIP, dysbiosis and endotoxemia [149]. A study with 237 NAFLD patients determined a significant association between the concentration of LBP and LPS with the presence of nonalcoholic steatohepatitis (NASH) and fibrosis [150]. The endotoxemia could be related to the common dysbiosis in NASH. It has been reported that more *Bacteroides* and *Ruminococcus* and fewer *Prevotella* colonies in the gut from NAFLD patients with severe NASH than without NASH [151]. These data show that endotoxemia could be a consequence of obesity, diet, IIP, and dysbiosis, which may contribute to the development of other metabolic diseases.

The present work shows that the consumption of the WD components, with a lot of amounts of ultra-processed products, as well as the excessive consumption of alcohol, can be triggers of having an IIP and dysbiosis, as described in Figure 7. The high consumption of sugars (glucose and fructose), ω-6 fatty acids, sodium, additives, alcohol, and gluten (for some people) increases IP and generates dysbiosis. Both intestinal problems originating from WD consumption could generate endotoxemia, bacterial translocation, and antigens in the blood. These factors could increase stimulated immune cells and proinflammation and, therefore, could promote the initiation, development, and prolongation of diseases, especially autoimmune and neurological ones [152, 153], which did not have greater relevance until a few years ago.

Based on the information provided, there is insufficient evidence to support the idea that the diseases outlined in this study contribute to IIP, or that IIP causes the diseases. However, there is a strong association between disease and IIP, although it is unclear which comes first. Therefore, future research should focus on reducing the likelihood of IIP, whether or not it is associated with a disease.

Consuming a diet low in WD components can help prevent IIP and dysbiosis in healthy individuals. Additionally, a healthy diet can serve as a supportive treatment for various diseases including neuroinflammatory, autoimmune, and metabolic conditions. Research studies have shown that incorporating certain dietary components, as a supplement or included in the diet, such as vitamin D, glutamine, ω-3 fatty acids, fiber, prebiotics, and probiotics or fermented foods, can improve IIP. These components are referred to as "strengthening dietary components" because they help to strengthen TJ proteins, reduce inflammation, and promote a healthy microbiota [154]. For example, foods rich in ω-3 fatty acids, such as fish and its oils, help their anti-inflammatory capacity [155]. Glutamine has been demonstrated as a supplement that reinforces TJ [156]. Due to their high fiber content, fermented foods, probiotics supplements, vegetables, legumes, and whole grains allow an adequate microbiota and a reduction in the entry of endotoxins [154]. And finally, fruits, vegetables, cereals, and beverages, such as red wine, can be useful due to their high polyphenols content (especially quercetin and resveratrol), which can modulate the TJ proteins expression [157]. These healthy components could be included in patient's diet with any disease described in this review (i.e., autoimmune, neurological, or metabolic disease) to strengthen the intestinal barrier.

As we have seen, consuming certain "strengthening dietary components" has been shown to have a positive effect on the intestinal barrier and reduce IIP. However, it is important to consider the best way to administer these components. We suggest that the first step in nutritional treatment for people likely to have IIP is to reduce the components of the WD before beginning any therapy with strengthening dietary components. For instance, in a study where probiotic triple viable capsule supplementation (*Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*) was evaluated to determine its effectiveness in patients with a high-fat diet, no significant improvement was observed when probiotics were added without changing the diet [158]. Therefore, it is not enough to introduce "strengthening dietary components" to improve the intestinal barrier if the damaged components are not reduced.

It is crucial for a health professional, such as a nutritionist, to be part of the patient's treatment and work in collaboration with the doctor to provide conventional treatment and consider possible intestinal problems that indicate IIP and dysbiosis in patients' clinical history. Initially, the nutritionist will assist in changing dietary habits and eliminating WD components that promote IIP. Subsequently, the

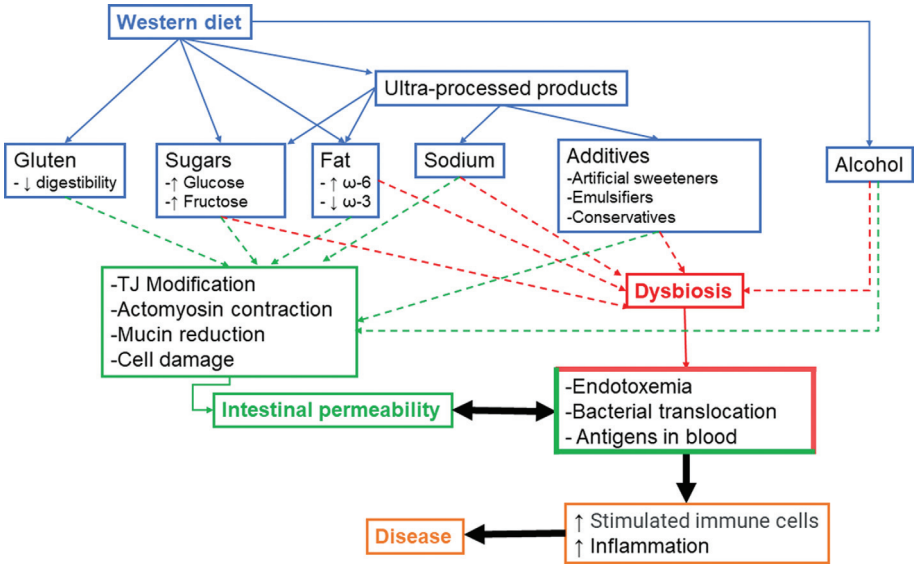

Figure 7. Dietary components increase intestinal permeability and its connection with the development of diseases. Blue lines are associated with WD components. The green square and green lines represent the association with the components and intestinal permeability (IP) development. Red lines are associated with the components that development of dysbiosis. The red/green square shows the interaction and effect of dysbiosis and intestinal permeability. The orange square represents the effect of IP/dysbiosis on the disease-causing system of the organism.

nutritionist will include foods rich in "strengthening dietary components" in the patient's diet. However, in the case of supplementation, it is essential to consider that more research is required to determine the appropriate doses and types of supplements. For example, a meta-analysis showed that supplementation of the *Lactobacillus rhamnosus* strain GG increased the relapse rates of Crohn disease [159]. Therefore, it is important to understand that not all probiotics are effective, and there are no established supplement dosages. A systematic review revealed that different doses of L-glutamine given to patients with inflammatory bowel disease did not significantly reduce intestinal permeability in most of the studies evaluated [160]. For this reason, it is essential to take special care when supplementing with certain components due to the lack of sufficient evidence regarding their effect on IIP; the effectiveness of a certain supplement will also depend on the type of disease the patient has. Therefore, we emphasize the importance of reducing WD consumption as it is an easy and cost-effective way to improve habits, leading to an overall improvement of not only the intestine but also neurological, autoimmune, or metabolic diseases the patient may have.

Conclusions

High consumption of certain components found in a WD, such as fructose, glucose, fat, sodium, alcohol, food additives, and gluten (in some people), can cause changes in the TJ, leading to IIP. Additionally, components present in the intestinal lumen can cause an imbalance in the gut microbiota, which in turn promotes heightened intestinal permeability. Although there is some evidence showing how dietary components can increase permeability, more research is needed to draw conclusions about humans. Nonetheless, it is clear that IIP can lead to the passage of endotoxins into circulation, which has been linked to certain diseases, including autoimmune, neuroinflammatory, or metabolic diseases. Therefore, medical specialists should consider the possibility of intestinal problems, such as intestinal permeability and dysbiosis, in the clinical history of patients with these diseases. Furthermore, nutritionists should modify the patient's diet by reducing or eliminating foods associated with a WD and increasing foods that can regulate and stabilize intestinal permeability and dysbiosis. These points should be considered in the future to improve the treatment of patients while always keeping in mind the importance of intestinal health in any disease.

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