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REVIEW ARTICLE

Food, gut barrier dysfunction, and related diseases: A new target for future individualized disease prevention and management

Linda Liang[1] | Clarissa Saunders[1] | Nerses Sanossian[2]

[1]University of Southern California, Los Angeles, California, USA

[2]Department of Neurology, Medical School of Southern California, Los Angeles, California, USA

Correspondence
Linda Liang, University of Southern California, Los Angeles, CA, USA.
Email: linda.liang@med.usc.edu

Abstract

Dysfunction of gut barrier is known as "leaky gut" or increased intestinal permeability. Numerous recent scientific evidences showed the association between gut dysfunction and multiple gastrointestinal tract (GI) and non-GI diseases. Research also demonstrated that food plays a crucial role to cause or remedy gut dysfunction related to diseases. We reviewed recent articles from electronic databases, mainly PubMed. The data were based on animal models, cell models, and human research in vivo and in vitro models. In this comprehensive review, our aim focused on the relationship between dietary factors, intestinal permeability dysfunction, and related diseases. This review synthesizes currently available literature and is discussed in three parts: (a) the mechanism of gut barrier and function, (b) food and dietary supplements that may promote gut health, and food or medication that may alter gut function, and (c) a table that organizes the synthesized information by general mechanisms for diseases related to leaky gut/intestinal permeability and associated dietary influences. With future research, dietary intervention could be a new target for individualized disease prevention and management.

KEYWORDS
diet, intestinal permeability, leaky gut, microbiota, tight junction

1 | INTRODUCTION

The gut barrier is the most important defense system of human body. The surface of intestinal tract is approximately 7000–8000m^2, the largest interface between human body and external environment (Bengmark, 2013; De Santis et al., 2015; Lopetuso et al., 2015; Suzuki, 2013). The gut barrier includes mucus layer, commensal microbiota, and single layer of intestinal epithelium. The 20-μm-thick layer of intestinal epithelium contains enterocytes, endocrine cells, microfold (M) cells, goblet cells, and Paneth cells in the small intestine (Farré et al., 2020; Kinashi & Hase, 2021). There are more goblet cells and no Paneth cells in the colon. Lamina propria and muscularis mucosa of intestinal mucosa support and articulate the epithelial layer. Under physiological circumstances, the epithelial cells are joined together by the tight junction (TJ) and the adherens junction (AJ), thus forming a contiguous and relatively impermeable membrane. TJ and AJ are protein complexes. TJ connects in the apex of adjacent cells to regulate ion, solute, and microbe diffusion across the gut barrier and maintain homeostasis (Seo et al., 2021). AJ is more basal than TJ.

Besides the role to link adjacent cells, AJ does actin cytoskeleton regulation, cell signaling, and gene transcription (Guo et al., 2007; Seo et al., 2021).

Impaired integrity of intestinal barrier and structure of the TJ barrier may trigger local or systemic inflammation and diseases. It results in increasing intestinal permeability which allows antigens, endotoxins, pathogens, and other proinflammatory substances to pass through intestinal barrier into circulation (Fukui, 2016). Ongoing studies showed that dietary factor, extra stress, and lack of physical activities could change gut microbiota, impair epithelial cell TJ and AJ, cause gut dysbiosis, and increase intestinal permeability (Lopetuso et al., 2015; Plaza-Díaz et al., 2020). Physical exercises regulate gut microbiota diversity; increase abundance of short-chain fatty acids (SCFAs); and provide long-term benefits to the gut barrier (Plaza-Díaz et al., 2020). Unexpected or prolonged psychological and physiological stress threatens intestinal barrier homoeostasis which responds through gut–brain axis, hypothalamic–pituitary–adrenal axis and sympathetic nerve system (SNS), leading to autoimmune and other disorders (Bajaj et al., 2019; Camilleri, 2019; Foster et al., 2017; Ilchmann-Diounou & Menard, 2020; Karl et al., 2017; Yue et al., 2017). Food provides nutrition to human body, and diet is also the most important factor to modify and regulate or influence diversity of gut microbiota. It may alter the intestinal barrier and impact gut homeostasis. Disruption of intestinal barrier and intestinal permeability may induce inflammatory states or diseases in multiple systems (Camilleri et al., 2019; Khoshbin & Camilleri, 2020).

Many measurement tools exist to measure intestinal permeability ex vivo and in vitro, such as Ussing chamber, assessing urinary excretion probes, like the lactulose:mannitol ratio (LAMA), sucralose, sucrose, PEG4000/400, and 51Cr-EDTA; bacterial-related tests, like assays of serum lipopolysaccharides (LPSs) and other bacteria toxins, using IgA/IgM responses to Gram-negative bacteria, plasma D-lactate, fecal Butyrate production, fecal Hemolysin test; tests for biomarkers like plasma citrulline, plasm FABP, plasma and urine α-glutathione S-transferase (αGST), serum zonulin enzyme-linked immunosorbent assay (ELISA), urine claudin-3, fecal calprotectin, and α1-anti-trypsin test; histological approaches like Western blot for TJ expression, Goblet cell analysis, and shedding of epithelium (Bischoff et al., 2014; Duerksen et al., 2010; Fasano, 2020; Odenwald & Turner, 2013); others like serum fluorescein isothiocyanate dextran (FITC-d; Vuong et al., 2021), and endomysial (EMA) and tissue transglutaminase (TTG) antibodies specifically for celiac disease (Duerksen et al., 2010), and so on. Human gut biopsies, confocal endomicroscopy, and endoscopic mucosal impedance also are used for assessing intestinal permeability (Bischoff et al., 2014; Camilleri, 2019). However, there are no current gold standard tests for gut barrier function (Camilleri, 2019).

Given the current lack of comprehensive review on how dietary therapy approaches can play an important role in the prevention, management, and treatment of diseases, we summarize dietary factors in this review.

2 | MECHANISMS OF INTESTINAL EPITHELIAL BARRIER

In a review of the current understanding, intestinal epithelium provides a dynamic permeable barrier to selectively absorb nutrients while simultaneously separating mucosal tissues from luminal commensal bacteria, pathogens, and dietary antigens. Epithelial barrier functions include functions of an apical TJ, subjacent junction AJ, and desmosome (Luissint et al., 2016). The imbalance of intestinal microbiota is known as gut dysbiosis, which causes increasing intestinal permeability or leaky gut syndrome (LGS). It directly or indirectly triggers immune system reaction. Functional food or non-functional food may change the intestinal microbiota bidirectionally (Ferreira et al., 2020).

2.1 | Physiological structure of epithelium and its function

A well-structured network of intestinal epithelial and stromal cells provides efficient nutrients and physical barrier against potentially harmful entities, including microorganisms, dietary antigens, or other noxious agents. There are multi-layer physicochemical barriers in the intestinal mucosa. The outer layer is the microbiota that competes and represses pathogens. The next is mucus layer, which contains antimicrobial peptides (AMPs) and secretory IgA. The mucus layer consists of gel-forming mucins including water and glycosylated proteins. It prevents microbiota and large molecules contacting the epithelial cells. The mucus layer in the colon forms a double layer, an inner and an outer layer. The third layer is a single layer of columnar epithelial cells (Seo et al., 2021). Epithelial stem cells can differentiate into four cells: enterocytes, goblet cells, enteroendocrine cells, and Paneth cells (in small intestine) and the intestinal epithelium renews approximately every five days (Bischoff et al., 2014). The 80% of epithelial cells are enterocytes which form an effective barrier to protect the internal milieu. The epithelial cells absorb beneficial molecules which include broken down proteins, fats, sugars, as well as water, electrolytes, vitamins, and bile salts from the gut lumen and transport them into the body. Enterocytes also secrete hormones such as leptin. Paneth cells are mainly located at the crypt and produce AMPs that play an important role in host immunity. Goblet cells secrete mucus forming a mucous layer. The enteroendocrine cells produce GI hormones (Bischoff et al., 2014; Farré et al., 2020). M cells are in the epithelium covering mucosa-associated lymphoid tissues, such as the Peyer's patches of small intestine. M cells actively transport luminal antigens to underlying lymphoid follicles to initiate an immune response (Allaire et al., 2018). The epithelial cells are interconnected tightly with TJ and AJ. The deep part of the gut barrier contains complex network of immune cells, known as gut-associated lymphoid tissue (GALT). The underlying lamina propria contains dendritic cells (DCs), intraepithelial DCs, macrophages, intraepithelial lymphocytes (IEL), T regulatory cells (T Regs), $TCD4^+$ lymphocytes, B lymphocytes, and plasma cells. Plasma cells release secretory immunoglobulin A (sIgA; Rescigno, 2011; Schenk & Mueller, 2008).

2.2 | Tight junction, adherens junction, and desmosomes

The essential role of intestinal epithelium is to separate intestinal luminal contents that leak to circulatory system (Odenwald & Turner, 2013). Intestinal epithelial cells are sealed by protein complexes of apical TJs, subjacent AJs and desmosomes (DMs). Epithelial barrier function is mediated by TJs, AJs, and DMs (Luissint et al., 2016). The TJ plays important role to maintain the intestinal permeability. The AJs along with desmosomes provide strong adhesive bonds between the epithelial cells, and also intercellular communication, but do not determine paracellular permeability (Suzuki, 2013). AJs and DMs mediate direct cell-to-cell contacts. The AJ's key transmembrane protein, E-cadherin, mediates calcium-dependent homotypic intercellular adhesions. Two proteins of AJ are nectin–afadin and cadherin–catenin complexes. The nectin–afadin are responsible for the maturation of AJ, and the E-cadherin-β-catenin interacts with components of the cytoskeleton, and provides organization and maintenance of AJ (Cardoso-Silva et al., 2019). DMs provide anchorage sites for intermediate filaments, which are important for the maintenance of tissue architecture, and provide mechanical strength to the epithelium (Luissint et al., 2016).

The TJ biochemical structure is as follows. The TJ consists of transmembrane proteins: claudin, occludin, tricellulin, junctional adhesion molecule-A (JAM-A), intracellular plaque proteins, such as zonula occludens (ZO), and cingulin (Lerner & Matthias, 2015; Suzuki, 2013, 2020). Claudins contain 27 tetraspan integral membrane proteins in humans. Claudins oligomerize in cis and trans, and provide diverse combinations and the complement in TJ strands influences cellular barrier function. Based on permeability, claudins have been grouped into barrier-forming isoforms (claudin 1, 3, 4, 5, and 18), which provide barrier to macromolecules and ions, thereby increasing barrier tightness, and pore-forming isoforms (claudin 2, 10, 12, 15), which select pores to ions and water, which increases paracellular permeability (Luissint et al., 2016; Suzuki, 2020). Claudins are responsible for TJ and epithelial barrier formation, constitution of TJ strands, and cytoskeleton organization (Cardoso-Silva et al., 2019). Occludin belongs to TJ-associate MARVEL domain-containing proteins (Luissint et al., 2016). Occludin is important in TJ stability and barrier function (Saitoa et al., 2021). Claudin and occludin form homotypic complexes between cells. The tricellulin junctions contact three adjacent cells and regulate the permeability of small ions and solutes. Tricellulin and occludin maintain epithelial barrier integrity by helping to form and stabilize TJ strand branching points (Saitoa et al., 2021). ZO proteins include ZO-1, ZO-2, and ZO-3. ZO proteins are scaffolding proteins which provide the structural basis for the assembly of multiprotein complexes at the cytoplasmic surface of intercellular junctions. ZO-1, 2, and 3 connect occludin and claudin to actin cytoskeleton and maintain the TJ formation (Suzuki, 2013, 2020; Zihni et al., 2016). JAM-A is an immunoglobulin superfamily (IgSF) – cell adhesion molecule (CAM). JAM-A recruit protein scaffolds to specific sites of cell–cell adhesion and assemble signaling complexes (Steinbacher et al., 2018). JAM plays a role in barrier regulation and TJ maintenance (Cardoso-Silva et al., 2019). Cingulin is an actin cytoskeleton-associated protein, and one role is for TJ assembly (Suzuki, 2013).

Impairment of intestinal TJ barrier causes increasing intestinal permeability, thereby resulting in intestinal and systemic inflammation and disorders. Currently, there are no effective therapies available that specifically target the tightening of the intestinal TJ barrier or no FDA-approved agents to treat the epithelial barrier dysfunction (Al-Sadi et al., 2021; Odenwald & Turner, 2017). According to research, using nutrition and dietary factors could effectively maintain and protect TJ barrier dysfunction. This review summarizes food influences on TJ barrier.

2.3 | Gut microbiota

Obrenovich et al. (Obrenovich et al., 2020) identified the novel name "holobiota" to describe all the microbiota that live within human's gut, including entire and diverse collection of microbes, mycobiota, commensals, pathogens, viruses, viroids, protozoan parasites, and their genomes, nucleic acid and so on. There are more than 100 trillion microorganisms which total 1–2 kg in mass in human's GI tract and each individual has a unique gut microbiota profile. The gut microbiota provides nutrient metabolism, participates in growth and immune regulation, eliminates pathogenic microorganisms, and maintains gut barrier integrity and normal homeostasis. Research shows that gut microbiota benefits the hosts by producing vitamins, preventing the growth of harmful bacteria, training the immune system, and fermenting unused food. The gut microbiota plays an important role in regulating the intestinal mucosa permeability and changing the microbial community impacts on gut mucosal barrier function. The bacterial population is currently the most well characterized in the literature. The more abundant and diverse the microbiota, the more powerful it is to fight external threats throughout the life for human being (Rinninella, Pauline Raoul, et al., 2019; Sung et al., 2016). The human gut virome mainly consists of bacteriophages, eukaryotic viruses, and other plant- and animal-derived viruses along with food (Carding et al., 2017). Viruses could be pathogenic or beneficial for the hosts. GI microbiota of healthy hosts has been detected following eukaryotic viruses' families: Adenoviridae, Anelloviridae, Astroviridae, Caliciviridae, Circoviridae, Coronaviridae, Parvoviridae, Picobirnaviridae, Picornaviridae, Polyomaviridae, and Reoviridae (Julio-Pieper et al., 2021).

The individualized microbiota is shaped in early life and its diversity increases with age until mature adult. The majority of GI tracts in stable adults are representatives of three main bacterial phyla: Firmicutes (Lachnospiraceae and Ruminococcaceae), Bacteroidetes (Bacteroidaceae, Prevotellaceae, and Rikenellaceae), and Actinobacteria (Bifidobacteriaceae and Coriobacteriaceae), which may be influenced by genetics, environment, diet, lifestyle, stress, and gut physiology (Maukonen & Saarela, 2015; Rea et al., 2020; Rinninella, Cintoni, et al., 2019; Tidjani Alou et al., 2016). In healthy human adults, the dominant five bacterial

phyla were reported as *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Among them, *Firmicutes* and *Bacteroidetes* account for more than 90% (Hansen & Sams, 2018). With the aging of the body, there are obvious changes in the diversity, structure ratio, and metabolism of gut microbes, leading to the imbalance of homeostasis, such as a decrease in anaerobic bacteria like *Bifidobacterium* spp. and an increase in *Clostridium* and *Proteobacteria* (Odamaki et al., 2016). Aside from age, there are other factors that affect the human gut microbiota, such as unbalanced diet, genetics, medications, and diseases (Maukonen & Saarela, 2015). The monozygotic twins have been reported with more similar microbiota than control group (Turnbaugh et al., 2010). Medication is an important external factor affecting human gut microbiota (Maukonen & Saarela, 2015). Daily exercises may increase resistance of the intestinal barrier through diversification of gut microbiota through a *Firmicutes* enrichment microbiota: Clostridiales, Roseburia, Lachnospiraceae, and Erysipelotrichaceae, producing SCFAs, with increased expression of TJ proteins (Bai, Hu, & Bruner, 2019; Monda et al., 2017).

A healthy gut microbiota is recognized as a relatively balanced state called normobiosis (Doré & G Corthier, 2010). Intestinal microbiota is significant for regulating the immune system during pathogenesis conditions, such as a decrease in bacterial diversity and an aberrant increase in some commensal bacteria (Al-Sadi et al., 2021). The imbalance of microbial communities in or on the body is called dysbiosis. Dysbiosis can alter metabolite profile because metabolites are produced by the microbiota (Ferreira et al., 2020; Kim, 2018; Raza et al., 2019; Tang et al., 2019). Altered balance in the host–microbe relationship may impair the development of the immune system, potentially leading to diseases (Patterson et al., 2014). The recent research has shown that imbalance of gut microbiota can cause a range of different diseases through following axes: Brain–Gut axis/Gut–brain axis (Camara-Lemarroy et al., 2018), Gut–brain-muscle axis (van Krimpen et al., 2021), Gut–brain neuroendocrine metabolic (GBNM) axis (Obrenovich, 2018), Gut–joint axis (Yang et al., 2016), Gut–kidney axis (Ondrussek-Sekac et al., 2021), Gut–liver axis (Plaza-Díaz et al., 2020; Preveden et al., 2017; Sung et al., 2016), Gut–liver–brain axis (Woodhouse et al., 2018), Gut–liver–immune system axis (Woodhouse et al., 2018), Gut–liver–kidney axis (Amornphimoltham et al., 2019), Gut–lung axis (Trivedi & Barve, 2020), Gut–retina axis (Rinninella et al., 2018), Hypothalamic–pituitary–adrenal (HPA) axis (Chu et al., 2018), Hypothalamic–pituitary–thyroid (HPT) axis (Krysiak et al., 2019), Microbiota–Gut–Immune–Glia (MGIG) axis (Rudzki & Maes, 2020), Thyroid–gut axis (Cayres et al., 2021; Knezevic et al., 1769), and other routes, through metabolism, inflammation, and immunity. Human enteric nervous system (ENS) is located within the gut wall and is connected with the enteroendocrine, GI immune system, the peripheral nervous system (PND), the central nervous system (CNS), and gut microbiota to regulate the intestinal epithelial barrier permeability and keep dynamic balance (Niesler et al., 2021; Neunlist et al., 2003). Diet may restore dysbiosis to normobiosis through immune regulation (Baraniya et al., 2020; Beliaeva et al., 2013).

2.4 | Immunological function of intestinal barrier

During gut microbiota–host interaction, gut releases cytokines, chemokines, neurotransmitters, neuropeptides, endocrine messages, and microbial byproducts including SCFAs, LPS, peptidoglycans, among others (Rea et al., 2020). Gut microbiota produce metabolites including carbohydrate metabolites, amino acid metabolites, and bile acid metabolites, which regulate host immune system through histone deacetylases (HDACs), G-protein coupled receptors (GPCRs), Aryl hydrocarbon receptor (AhR), and so on, to regulate neutrophil chemotaxin, macrophages, DCs, T-Cells, IgA and IgG, and cytokines. The results can be barrier function and tolerance or inflammation (Kim, 2018).

In the human colon, anaerobic fermentation of undigested nutrients, such as dietary fiber, resistant starch, and complex polysaccharides can be recognized by GPCRs and metabolized by the microbiota, resulting in the synthesis of SCFAs. SCFAs are the major metabolic products of coliform bacteria. SCFAs contain <6 carbon chains, including acetate (60%), propionate (25%), and butyrate (15%), which consider the major energy substrate for colonocytes to maintain intestinal barrier integrity and homeostasis. SCFAs fuel and fortify epithelial cells, regulate macrophages and DCs through GPCRs and HDACs, and also fuel B cells and promote their differentiation into IgA/IgG-producing plasma B-cells. SCFAs may influence GI and systemic health through immunomodulatory and anti-inflammatory effects. It can induce immune tolerance via Treg cells. Recent studies have shown that SCFAs can maintain normal colorectal function by regulating the metabolism of colon cells, thereby preventing the occurrence of diseases (Ferreira et al., 2020; Kim, 2018; Rinninella, Cintoni, et al., 2019; Tang et al., 2019).

LPS, peptidoglycans, muramyl-dipeptides, bacterial DNA, etc. are produced by bacteria and translocated from the gut to mesenteric lymph nodes. Gram-negative bacteria have outer membranes, in part comprised of LPS, also known as a bacterial endotoxin. LPS can increase immune permeability, cross immune barrier, and result in inflammation. LPS can alter signaling of Toll-like receptors (TLRs), related to leaky gut syndrome (Obrenovich et al., 2020; Plaza-Díaz et al., 2020; Sperandeo et al., 2017).

Cytokines are produced by lymphokines, monokines, chemokines, interleukins, interferons, colony-stimulating factors, and growth factors. Cytokines involve regulation of immune system pathways (Ramani et al., 2015). The main proinflammatory cytokines are interleukin (IL)-1β, IL-6, IL 12, tumor necrosis factor-α (TNFα), interferon- γ (IFN- γ), and nuclear factor kappa-activated B cells (NF-κB) and the main anti-inflammatory cytokines are IL 4, 10, 11, 13, and transforming growth factor-β (TGF-β). Proinflammatory cytokines cause a disturbance in intestinal TJ barrier, allowing increased intestinal permeability (Bamias et al., 2012; Fang, 2018; Opal & DePalo, 2000; Ramani et al., 2015; Seo et al., 2021).

The host innate immune system detects microorganisms and responds to their stimuli mainly through recognition of TLRs. TLRs recognize invading microbes and activate immune cell response.

TLRs are crucial in the innate response to pathogens, in that they recognize and respond to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which lead to activation of intracellular signaling pathways and altered gene expression. Myeloid differentiation factor 88 (MyD88) is the key adaptor protein for intracellular signaling that mediates multiple TLRs. The host innate immune system detects microorganisms and responds to their stimuli mainly through recognition of TLRs (Kawasaki & Kawai, 2014; Mukherjee et al., 2016).

Intestinal epithelial mucus contains AMPs such as α- and β-defensins secreted by Paneth cells and sIgA at mucosal surfaces which can protect from invasion of pathogens like coating bacteria, fungi, and enveloped virus, and neutralize bacterial toxins (Camilleri et al., 2019; Ouellette, 2010; Pabst, 2012).

Many factors can alter intestinal permeability such as dietary factors, epithelial damage, mucus layer dysfunction, and gut microbiota modification (Bischoff et al., 2014). Environmental factors like diet or drugs may cause dysbiosis, which impairs epithelial barrier function and elicits proinflammatory cytokines. This process damages TJ integrity and increase gut permeability, leading to leaky gut syndrome (Lopetuso et al., 2015). Compromised intestinal barrier function has been associated with intestinal and systemic diseases (Odenwald & Turner, 2017).

3 | FOOD/FOOD COMPONENTS AND DIETARY SUPPLEMENTS MAY PROMOTE GUT HEALTH AND FUNCTION

Diet or food-derived compounds and their metabolites may have broad effects for regulating gut microbial composition and intestinal permeability directly or indirectly; however, those effects are not thoroughly understood. The diversity of gut microbiota has been implicated in the synthesis of vitamins, secondary bile acids, neurotransmitters, and metabolism and degradation of dietary components (Camilleri et al., 2019; Peron et al., 2020).

3.1 | Diets

3.1.1 | Mediterranean diet

Mediterranean diet (MD) was first described by the nutritionist Ancel Keys in 1945 and people who live in Spain, Greece, Southern Italy, and other countries facing the Mediterranean basin have MD as a typical dietary habit. MD includes high intake of fruits, vegetables, legumes, nuts, and minimally processed cereals, moderate high consumption of fish and olive oil, low-to-moderate intake of wine during meals, low-to-moderate amount of yogurt and cheese, and low consumption of saturated fats, red meat, and meat products. MD contains high level of antioxidants, polyunsaturated fatty acids (PUFAs), monounsaturated fatty acid (MUFA), and polyphenols. The main fat of MD is from extra-virgin olive oil (EVO). The EVO is the key component of MD which can interfere with arachidonic acid and NF-κB signaling pathways and ameliorate intestinal permeability. The EVO may decrease IL-1β, TGFβ, IL-6 and decrease chronic inflammation. Research demonstrated that MD increases SCFAs, microbiota diversity and stability, such as increasing *Bifidobacteria*, *Lactobacillus*, Lachnospiraceae, and *Bacteroidetes* and decreasing *Clostridium* and *Enterobacteria*. MD increases IL-10 and IL 22, and decreases IL-17, and therefore improves immune function. Studies showed that MD is beneficial for obesity, type 2 diabetes, inflammatory diseases, cardiovascular diseases, stroke, cancer, Parkinson's disease, and Alzheimer's disease (Braga et al., 2013; Cariello et al., 2020; Filippis et al., 2016; Laura Soldati et al., 2018; Lourida et al., 2013; Psaltopoulou et al., 2013; Rinninella, Cintoni, et al., 2019; Sofi et al., 2008).

3.1.2 | Ketogenic diet

Ketogenic diet (KD) was established in the 1920s and continues to be used worldwide for the treatment of drug-resistant epilepsy, which is about one-third of epilepsy patients (Fan et al., 2019), especially for pediatric epilepsy patients (Arulsamy et al., 2020). KD is a high-fat, sufficient protein and very low-carbohydrate diet and the fat to protein and carbohydrate ratio is about 4:1 (Dahlin & Prast-Nielsen, 2019). Studies showed that KD made a significant difference in gut microbiota diversity: decreasing *Bifidobacteria*, *Eubacterium rectale*, *Dialister*, Proteobacteria, and *Firmicutes*, and increasing *Enterobacteria*, *Desulfovibrio* spp, *Parabacteroides*, *Bacteroidetes*, *Actinobacteria*, and *Akkermansia* (Arulsamy et al., 2020; Rinninella, Cintoni, et al., 2019). However, it may decrease total bacteria abundance and decrease SCFAs (Rinninella, Cintoni, et al., 2019). Epilepsy could be triggered by commensal microbiota via elevating IL-6 and IL-1β and driving Th17 responses. KD has been shown to improve epilepsy frequency or duration (Arulsamy et al., 2020). Very low-carbohydrate KD can decrease serum levels of glucose and insulin growth factor (IGF) and delay cancer progression. Gut microbiota influences the brain through endocrine, immune, and metabolic systems via MGB/GMB axis. In addition to epilepsy, KD is beneficial for Glucose transporter 1 (GLUT1) Deficiency Syndrome, autism spectrum disorder, obesity, cancer, migraine, glaucoma, multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Unfortunately, long-term use of KD may have some adverse effects, including constipation, hypercholesterolemia, etc. It has been recommended to add probiotics, vitamins, and minerals to KD (Ersoz Alan & Gulerman, 2019; Fan et al., 2019; Laura Soldati et al., 2018; Olson et al., 2018; Rinninella, Cintoni, et al., 2019; Tagliabue et al., 2017).

3.1.3 | Low-FODMAP diet

Low fermentable oligosaccharide, disaccharide, monosaccharides, and polyols (FOMAP) diet was created by Monash University in

2004 (Rinninella, Cintoni, et al., 2019). FODMAPs are a group of carbohydrates from fructose, fructans, lactose, polyols and galactooligosaccharides that are poorly absorbed in small intestine and subsequently fermented in the small or large intestine which cause GI discomfort and symptoms. High-FODMAP diet includes grains: wheat-, rye-, barley-based grains, semolina, etc.; fruits: ripe banana, apples, pears, cherries, watermelon, peaches, mango, dry fruits, etc.; vegetables: artichokes, onion, garlic, leeks, asparagus, cauliflower, beetroot, peas, etc.; dairy: cow's milk, ice cream, soy milk, yogurt, soft cheese, etc.; nuts, seeds, and legumes: baked beans, butter beans, kidney beans, soybeans, lentils, etc. Low-FODMAP diet includes grains: gluten-free products, quinoa, amaranth, brown rice, bulgur, etc.; fruits: small firm banana, avocado, blueberries, strawberries, raspberries, kiwi, lemon, oranges, papaya, pineapple, etc.; vegetables: broccoli, carrots, arugula, kale, lettuce, spinach, tomatoes, zucchini, etc.; dairy and alternatives: lactose free, almond, coconut or rice-based milk, hard or aged cheese, etc.; nuts, seeds and legumes: almonds, hazelnuts, macadamia nuts, pecans, pine nuts, walnuts, chia seeds, pumpkin seeds, sesame seeds, sunflower seeds, etc. Peeled apples and pears are included in the low-FODMAP Diet. Excessive intake of FODMAP causes bacteria overgrowth in small intestine which increase intestinal permeability and induce colon epithelial irritation or injury. Low-FODMAP diet decreases total bacteria abundance, such as decreasing *Bifidobacteria*, *Ruminococcus gnavus*, *Clostridium*, *F. prausnitzii*, and *Akkermansia*. Low-FODMAP diet has been used to treat inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS; Guagnozzi et al., 2012; Martín et al., 2022; Mazzawi et al., 2013; Nanayakkara et al., 2016; Ostgaard et al., 2012; Rinninella, Cintoni, et al., 2019).

3.2 | Probiotics & prebiotics

3.2.1 | Probiotics

According to the FAO/WHO, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO, 2002). The main currently used probiotic blend contains the most commonly lactic acid-producing *Bifidobacterium* and *Lactobacillus* spp. (Maukonen & Saarela, 2015). The action of probiotics includes increasing microbial diversity, competing with pathogens, producing bacteriocin, producing vitamins and SCFAs, enhancing immunity such as increasing IgA and C-creative protein (CRP) and increasing anti-inflammatory cytokine production like IL-10 reducing intestinal permeability and oxidative stress, improving the mucosal integrity and barrier function, and producing neurotransmitters (Angelisa et al., 2019; Ballan et al., 2020; Kim, Keogh, & Clifton, 2018; Singh et al., 2017). Probiotics are also effective for small intestinal bacterial overgrowth (SIBO) decontamination and symptom relief (Judkins et al., 2020). Research demonstrated evidence of positive effects by using probiotics for gut microbiota restoration and modulation in gut dysbiosis (Hills Jr. et al., 2019; Marasco et al., 2020; Sharma & Singh, 2016; Singh et al., 2017).

Fermented food contains probiotics, prebiotics, and biogenics (functional metabolites). Fermented foods can produce vitamins, lacto-try-peptides, bacteriocins, and immunopotentiators during process of fermentation (Aslam et al., 2020). Fermented food shows a significant positive improvement in balancing intestinal permeability and barrier function (Bell et al., 2018). Main probiotic foods are yogurt, kefir, sauerkraut, tempeh, kimchi, miso, kombucha, pickles, traditional butter milk, soy sauce, natto, and cheese (Aslam et al., 2020; Marco et al., 2017)

Yogurt

Research has shown that yogurt can reduce counts of the enteropathogens *E. coli* and *Helicobacter pylori* (Liu et al., 2010; Yang & Sheu, 2012). Yogurt increases *St. thermophilus*, *L. delbrueckii* ssp. and *Bulgaricus* (Marco et al., 2017). Yogurt can reduce Caco-2 transepithelial electrical resistance (TEER), modulate intestinal barrier function by improving occludin and ZO-1 at TJ and preventing trinitrobenzene sulfonic acid-induced intestinal inflammation, and reduce TLR4 (Putt et al., 2017). Yogurt can improve fasting blood glucose and antioxidant status for type 2 diabetes (T2DM) patients (Ejtahed et al., 2012).

Kimchi

Kimchi is one of most popular Korean side dishes made from fermenting vegetables, and various ingredients like red pepper powder, garlic, ginger, green onion, fermented seafood, and salt, which contain beneficial microbiota (Kim, Keogh, & Clifton, 2018; Shin et al., 2016). Kimchi has been reported by Health Magazine in 2006 as one of the five world's healthiest foods (Dharaneedharan & Heo, 2016; Patra et al., 2016). Research showed that the fermented kimchi is healthier than fresh kimchi (An et al., 2013). Fermented kimchi showed positive effects including improvement of metabolic function, lipid metabolism, insulin resistance/sensitivity, systolic and diastolic blood pressure, and enhancement of immune response (Han et al., 2015; Kim et al., 2011; Shin et al., 2016). Kimchi has anti-inflammatory, antibacterial, antioxidant, anticancer, antiobesity, probiotic properties, cholesterol reduction, and antiaging properties (Patra et al., 2016). Kimchi increases *Lu. mesenteroides*, *L. plantarum*, and *L. brevis* (Marco et al., 2017).

3.2.2 | Prebiotics

Prebiotics have been defined as "selective fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host well-being and health" (Gibson et al., 2004) and selectively promote beneficial bacteria, mainly *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii* (Marasco et al., 2020; Maukonen & Saarela, 2015; Scott et al., 2013). Those beneficial microbes have a function of anti-inflammation, improvement of gut barrier and gut health. Prebiotics increase SCFAs and IL-10 and decrease LPS and IL-6 (Singh et al., 2017). The important dietary fibers, such as

fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides (IMO), xylo-oligosaccharides (XOS), arabino-xylo-oligosaccharides (AXOS), pectic-oligosaccharides (POS) and resistant starch (RS) pass undigested through the GI tract until reaching the colon to be fermented by gut microbiota. Prebiotics include FOS, GOS, XOS, IMO, lactulose, and polysaccharides like inulin, RS, cellulose, etc. FOS, XOS, and AXOS improve the metabolic activity of intestinal microbiota, and decrease the synthesis of protein-derived toxic compounds, such as pcresol, phenol, biogenic amines (Angelisa et al., 2019; Hills Jr. et al., 2019; Maukonen & Saarela, 2015; Yan et al., 2018; Yao et al., 2016). Inulin is a soluble fiber and fructans, which can normalize glucose tolerance or lipid profile (Kim, Keogh, & Clifton, 2018). Prebiotics enriched foods are artichokes, onions, garlic, leeks, soybeans, chicory roots, honey, banana, seeds, and selective fibers (Kim, Keogh, & Clifton, 2018; Maukonen & Saarela, 2015).

Synbiotics

Synbiotics are mixtures of probiotics and prebiotics. Synbiotics have shown effects for celiac disease, T2DM, nonalcoholic fatty liver disease (NAFLD), liver cirrhosis and steatosis, muscle wasting and many other diseases (Kim, Keogh, & Clifton, 2018; Marasco et al., 2020; van Krimpen et al., 2021; Woodhouse et al., 2018). Probiotics, prebiotics, and synbiotics have been shown to restore immunity, correct altered intestinal microbiota, balance the equilibrium between TREG and Th17 cells, and maintain human normal health state (Amati et al., 2010; Angelisa et al., 2019).

3.3 | Fruits and vegetables

High dietary intake of fruits and vegetables can reduce risks of diseases by multiple factors (Amasheh et al., 2009). Fruits, vegetables, and other plant-derived food like tea and juice contain phytochemicals including major compounds such as polyphenols including flavonoids like anthocyanins (ACNs) and quercetin, resveratrol, epigallocatechin gallate (ECGC), and curcumin, carotenoid, organosulfur compounds, phytoestrogens, etc. Phytochemicals can reduce intestinal permeability and improve intestinal function through reducing proinflammatory cytokines and increasing anti-inflammatory cytokines, increasing beneficial bacteria, and reducing pathogenic bacteria. Phytochemical can also reduce NF-κB and signal transducer, activate transcription (STAT), myosin light chain kinase (MLCK), and mitogen-activated protein kinase expression, and increase antioxidant activity and improve disease activity index (DAI) score (Hossen et al., 2020). Dietary phytochemicals can regulate miRNA and play a tumor suppressor role (Budisan et al., 2017).

Polyphenols are well-known antioxidants created by forming stable phenoxyl radicals and disrupting chain oxidation reactions in cellular components. The main sources of polyphenols are fruits, tea, and vegetables. Polyphenols may modulate the gut microbiota like stimulating *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii* and inhibiting *Helicobacter pylori*, *Staphylococcus aureus*, and *Listeria monocytogenes* (Manach et al., 2005; Septembre-Malaterre et al., 2018; Kumar Singh et al., 2019). Polyphenols can prevent or limit oxidative damage to cell components, DNA, protein, and lipids accumulation that are related to aging-associated diseases: CVDs, degenerative diseases, osteoporosis, and cancer (Parkar et al., 2008; Scalbert et al., 2005). Polyphenols have antioxidant and anti-inflammatory properties because polyphenols can reduce oxidative stress, reactive oxygen species (ROS), endothelial nitric oxide synthase (eNOS), nitric oxide (NO), and decrease intercellular cell adhesion molecule-1 (ICAM-1), vascular endothelial adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1(MCP-1), TNFα, IFN- γ, IL-6, IL-8, and NF-κB (Khurana et al., 2013). ROS is responsible for developing DM, CADs, and other age-related diseases such as Parkinson's and Alzheimer's disease (Selvaraju et al., 2012). The colors of fruits and vegetables are from ACNs. ACN-rich fruits and vegetables like strawberries, blueberries, blackberries, cherries, plums, grapes, red apples, red beets possess antidiabetic, anticancer, anti-inflammatory, antimicrobial, and antiobesity effects and preventing CVDs. Anthocyanin-rich bilberry extract can decrease inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines like TNFα, IFN- γ, and increase anti-inflammatory cytokines like IL-10, IL-22, and Th17 (Ghosh & Konishi, 2007; Lee et al., 2017; Lin et al., 2017; Manolescu et al., 2019; O'Donovan et al., 2019; Roth et al., 2016; Silva et al., 2016; Tsuda, 2016). Resveratrol is a stilbene compound and a phytoalexin found in plants such as red grapes, blueberries, red wine, ports, sherries, peanuts, itadori tea, hops, and pistachios (Burns et al., 2002). Resveratrol contributes a wide range of healing and preventive functions like cardiopreventive, neuropreventive, antitumor, and antioxidant roles (Gatuillat et al., 2010). Quercetin showed decreasing intestinal permeability through enhancing TJ function with claudin-1, claudin-4, ZO-2, and occludin in human intestinal CaCo-2 cells (Suzuki & Hara, 2009). A polyphenol-rich beverage, green tea, has been reported to alleviate inflammatory and hypersensitive disorders like metabolic syndrome and IBD. The green tea's major components are EGCG and catechins which may neutralize proinflammatory cytokines, diminish oxidative stress to epithelial cells, and decrease intestinal permeability (Peron et al., 2020; Van Buiten et al., 2018; Watson et al., 2004).

3.4 | Omega-3 fatty acids

Diets rich in PUFAs, especially ω−3FAs have positive health benefits. Unsaturated fatty acids (UFAs) include MUFA with one double-bond like omega-9 fatty acids (ω−9FAs). PUFAs have more than one double-bond such as ω−3FAs and ω−6FAs, and cis- and trans-fats (Simopoulos, 2002). ω−3FAs are mainly available in eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and docosapentaenoic acid (DPA). ω−3FAs have positive effects or prevent DM, IBD, CADs like MI and acute coronary syndrome, central nervous system diseases like dementia and depression through gut–brain axis,

autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis and psoriasis, carcinogenesis, and infections (Ballan et al., 2020; Merendino et al., 2013; Noriega et al., 2016; Watanabe & Tatsuno, 2017). A high ω−3FAs diet has the potential of increasing *Bifidobacterium*, *Lactobacillus* population, and SCFAs release (Robertson et al., 2017). Consumption of ω−3FAs has been reported to decrease serum triglycerides (TGs) and increase high-density lipoprotein cholesterol (HDL-C). ω−3FAs have anti-inflammatory properties such as suppressing TNFα, IL-1β, IL-6, and producing anti-inflammatory lipid mediators (E-series resolvins, D-series resolvins, protectins, and maresins). However, more research is needed to fully elucidate (Kaliannan et al., 2015; Miles & Calder, 2012; Watanabe & Tatsuno, 2017).

3.5 | Some other dietary supplements

Vitamins and minerals play a very important role in the regulation of GI homeostasis, especially vitamin A and vitamin D. Research showed that Vitamin A inhibited LPS and enhanced TEER, so preventing inflammation. Vitamin A strengthened ZO-1, Occludin, and claudin-1, while vitamin D increased ZO-1, claudin-1, claudin-2, and E-cadherin, thereby enhancing TJ and intestinal permeability. Vitamin D may have long-term implications for immune system modulation (Bischoff et al., 2014; Farré et al., 2020; Kong et al., 2008; Rinninella, Cintoni, et al., 2019). Minerals are involved in numerous bacterial physiological processes that impact the gut microbiota. Zinc is necessary to maintain expression of ZO-1, occludin and intestinal barrier function. Zinc deprivation increases intestinal permeability by reducing TER and altering TJ and AJ with delocalization of ZO-1, occludin, β-catenin, E-cadherin, and F-actin. Its depletion may also cause infectious diseases. Zinc is an important component of DNA polymerase and enzymes involved in cell replication and differentiation (Amasheh et al., 2009; Finamore et al., 2008).

4 | FOOD/FOOD COMPONENTS OR MEDICATION MAY ALTER GUT FUNCTION

4.1 | Western diet

Western diet is rich in saturated fatty acids, high glycemic-index sugars, especially fructose, refined carbohydrate, high salt, poor in fiber, and also includes processed food. The negative effects include high energy load, inadequate energy balance, and changing gut microbiota (Bischoff et al., 2014; Manzel et al., 2014; Riccio & Rossano, 2015). Saturated fats (SFAs) include very long-chain fatty acids (VLCFAs) like arachidic acid (C20), long-chain fatty acids (LCFAs): [like stearic acid (C18), palmitic acid (C16), myristic acid (C14), and lauric acid (C12)], and medium-chain fatty acids (MCFAs) like caproic acid (C6) and SCFAs. Main dietary fats in high-fat diet (HFD) are LCFAs (Rohr et al., 2020). HFD changes gut microbiota, promotes LPS, stimulates TNFα, IL-1β, IL-6, IFN- γ, and decrease IL-10, IL17, and IL-22 directly or indirectly. Additionally, HFD increases susceptibility to food allergy. Overall, diets rich in SFAs are associated with negative health impacts (Bischoff et al., 2014; Ke et al., 2020; Rohr et al., 2020; Shi et al., 2019). The major route of high sugar consumption is through the apical transient insertion of glucose transporter type 2 (GLUT2)-mediated sugar absorption (Kellett et al., 2008). Fructose, glucose, and sucrose, especially fructose, increase intestinal permeability through altering TJ proteins like occludin, ZO-1, claudin 1 and 4, and interacting with cytochrome P450-2E1 (CYP2E1; Binienda et al., 2020). High fructose or glucose intake correlates with detrimental health outcomes, such as obesity, metabolic disorders, and hepatic steatosis (Do et al., 2018). Western diet decreases microbiota diversity, such as decreasing *Bifidobacteria*, *Roseburia*, *Eubacterium rectale*, *Ruminococcus bromii*, *Lactobacillus*, and *Prevotella* and increasing *Ruminococcus torques*, *Enterobacteria*, *Bilophila*, *Alistipes*, *Bacteroides*, and *Akkermansia*. Western diet increases LPS and proinflammatory cytokines, such as IL-17, TNFα, and IFN- γ, and decreases Treg/Th17 ratio and SFCAs, and therefore causes chronic inflammation and autoimmune diseases (Riccio & Rossano, 2015; Rinninella, Cintoni, et al., 2019). Individuals consuming Western diet showed depleted metabolic fuels, dysbiosis, and leading to high levels of endotoxin in plasma (endotoxemia). It increases gram-negative bacteria-related LPS and induces inflammation via TLR2 and TLR4 (Bengmark, 2013). Western diet contains excessive ω−6FAs and deficient ω−3FAs. It increases ω−6FAs/ω−3FAs ratio from 1:1 to 4:1 (normal) to 10:1 to 50:1 and thus promotes the pathogenesis of many chronic diseases like CADs, cancer, inflammatory, and autoimmune diseases (Kang, 2011; Simopoulos, 2008). It can increase translocation of bacteria and bacteria products in the intestine, and then enhance endotoxin in the portal vein, leading to low-grade liver inflammation (Bischoff et al., 2014).

Processed foods/industrial foods are detrimental to human health (Zinöcker & Lindseth, 2018). The thermal process of mixing amino acids and sugar generates advanced glycation endproducts (AGEs). AGEs can pass through GI tract to colon and alter gut microbial metabolism (Aljahdali & Carbonero, 2019; Hellwig & Henle, 2014). Almost all processed foods contain artificial sweeteners to improve the taste and texture, which can alter gut microbiota (Spencer et al., 2016; Suez et al., 2014). Chronic consumption of processed foods can compromise TJ protein, increase serum LPS, and impact intestinal permeability, causing multiple diseases, such as CADs, microvascular diseases like chronic kidney disease (CKD), obesity, DM, and cancer (Fiolet et al., 2018; Rico-Campà et al., 2019; Snelson et al., 2021).

Dietary additive emulsifiers are widely used in bakery, confectionary, dairy, ice cream, sauces, butter, gum, beverages, chocolate, and convenient food industries. The major food additive emulsifiers include lecithin, mono-and diglycerides of FA, guar gum, xanthan gum, carrageenan, celluloses, and polysorbates (Cox et al., 2021; Partridge et al., 2019). Dietary emulsifiers decreased gut microbiota diversity, decreasing anti-inflammatory genera *Akkermansia* and *Lupinus*, promoting proinflammatory genera *Escherichia*, *Roseburia*, *Bradyrhizobium*, and *Turicibacter*, and developing dysbiosis (Jiang

et al., 2018). Emulsifiers stimulate various inflammatory pathways, such as activating LPS-induced inflammation through Bcell lymphoma/leukaemia-10 (Bcl-10) pathway, and triggering NF-κB through TLR4 pathway, and increasing TNFα, IL-1β, IL-6, IL-8 pathway (Bancil et al., 2021). Emulsifiers can drop hydrophobicity of the mucus layer, reduce mucus thickness, and alter ZO-1 to allow bacteria translocation, which is associated with increasing intestinal permeability (Csáki, 2011).

4.2 | Gluten

Gluten is a main storage protein in wheat and is also contained in non-wheat cereals like barley, rye, and oats. Wheat contains nonprotein components like FODMAPs as well. Gluten proteins can be divided into alcohol-soluble gliadins and insoluble glutenins (Khoshbin & Camilleri, 2020; Vader et al., 2003; Wieser, 2007). The adverse effects of gluten through human gut post-translational modification of proteins (PTMP) and dysbiota mechanisms include the following: increasing systemic inflammation, oxidative stress, impacting systemic epigenetics, altering TJ and impacting microbiome, decreasing cellular viability, cell differentiation, and synthesis of DNA, RNA, and glycoprotein. Research also demonstrates that gluten increased apoptosis in cellular effects, increased immunogenicity and cytotoxicity, Th17 activity, neutrophil migration, natural killer group 2D (NKG2D) costimulatory molecule, TLR4 signaling pathway, changing innate and adaptive immune system functions, and Treg functions in immune effects (Fasano, 2020). Gluten impairs function of the TJ, AJ, DMs, and the colon mucosa, translocates bacteria, and elevates intestinal permeability (Menta et al., 2019). Dietary wheat germ agglutinin (WGA) induces the production of TNFα, IL-1β, IL-12, and IFN- γ, and can cross intestinal barrier or increase intestinal permeability (Pusztai et al., 1993; Sodhi & Kesherwani, 2007). Wheat proteins are also responsible for celiac disease (CD) and other gluten-/wheat-sensitive or intolerance conditions like IBD and IBS, and are associated with many other diseases due to chronic inflammation, such as CADs, metabolic syndrome, cancer, autoimmune diseases, neurological diseases like multiple sclerosis, dementia, schizophrenia, and depression. It is also responsible for baker's asthma, rhinitis, and contact urticaria though IgE-mediated allergic reactions (Barnes & Adcock, 2009; Cardoso-Silva et al., 2019; Fasano, 2020; Jonnalagadda et al., 2011; Tatham & Shewry, 2008). Gluten is clearly implicated damaging gut barrier in CD, and consequently, a gluten-free diet (GFD) is the only available treatment for CD (Al-Toma et al., 2019; Khoshbin & Camilleri, 2020). GFD increases *Bifidobacteria*, Victivallaceae, and *Enterobacteria*, and decreases Coriobacteriaceae, Veillonellaceae, *Ruminococcus bromii*, *Roseburia*, *Lactobacillus*, *Clostridium lituseburense*, and *F. prausnitzii*, and regulates the immunomodulatory role via cytokine induction of IL-10, TNFα, and IFN-γ (Rinninella, Cintoni, et al., 2019). However, even with a GFD, the abundance of gut bacterial population is different in normal individuals, CD patients, and nonceliac gluten-/wheat-sensitive patients (Caio et al., 2020).

4.3 | Medications

Oral antibiotics can cause acute or long-term effects due to eliminating antiproteolytic bacteria and increasing proteolytic activities in the colon (Yoon et al., 2018). In general, antibiotics change gut microbiota, implicate dysbiosis, impair gut barrier, and cause intestinal inflammation like Crohn's disease (Grigg & Sonnenberg, 2017; Hills Jr. et al., 2019; Yoon et al., 2018). The central mechanism of nonsteroidal anti-inflammatory drugs (NSAIDs) suggests induced intestinal hyperpermeability and causes small bowel disease (Bjarnason & Takeuchi, 2009; Ganda Mall et al., 2020). NSAIDs damage enterocytes through biochemical processes. Then luminal substances like bile acids, bacterial degradation products, acid, and pepsin have access to mucosa, resulting in inflammation due to increased intestinal permeability. With long-term use of NSAIDs, the inflammation may progress to GI ulcer, bleeding, or perforation (Bjarnason & Takeuchi, 2009). Proton pump inhibitors (PPIs), antipsychotic medications, opioids, and statins influence the gut microbiome and are detrimental to gut barrier and function (Imhann et al., 2016; Le Bastard et al., 2018).

4.4 | Lectins, aquaporins, heated vegetable oils, and food antigens

A lot of common foods like tomatoes, potatoes, eggplants, bell peppers, legumes, etc. are known as healthy foods. However, research shows some contradictory evidence. Legumes and nightshades (tomatoes, white potatoes, eggplant, peppers, and seed species) contain lectin. Lectins can increase intestinal permeability and increase innate immune cell activation, which may be associated with rheumatoid arthritis (RA) symptoms (Cordain et al., 2000). Soybean meal-based diets alter TJ protein mRNAs and decrease protein absorption, induce intestinal neutrophil turnover, and increase intestinal permeability in zebrafish (Solis et al., 2020). Dietary aquaporins (AQPs; corn, soybean, spinach leaf, and tomato AQP) may be mistaken for human aquaporin (AQP4) and the antibodies can cross-react with brain astrocytic endfeet, breaking blood–brain barrier (BBB), leading to neuro-autoimmunity and neurodegeneration, and cause neurological disorders, such as Alzheimer's disease, multiple sclerosis, and autism spectrum disorders. Individuals who lose their immune tolerance can remove the food AQPs and may improve the clinical conditions (Lambert et al., 2018). Soybean oil is the major oil in Western diet and contains more than 85% of ω−6FAs (Liu et al., 2014). The prolonged consumption of heated soy oil, and palm oil, or heated vegetable oils can cause hypertension and promote oxidative stress due to biochemical and vascular mechanisms such as impaired endothelium-dependent and endothelium-independent vasorelaxation as well as increased vasoconstriction responses (Leong et al., 2010; Siti et al., 2019). Vegetable oils have high ω−6/ω−3FAs radio which is a risk factor for health. Long-term ingestion of heated vegetable oil including fried food can lead to obesity, T2DM, and CVD or hypertension and other lifestyle-related diseases

TABLE 1 General mechanisms for diseases related to leaky gut/increased intestinal permeability and associated dietary influences.

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Dermatological disease			
General	Dietary allergy & environmental factors ➔ gut microbiome sensitivity ➔ dysbiosis ➔ LGS ➔ disturb skin ecosystem ➔ cause multiple skin conditions: Acne (two major bacteria: *Propionibacterium acnes* & *Staphylococcus epidermidis*), aging skin (also exposure to UV), psoriasis, atopic dermatitis, eczema, seborrheic dermatitis, vitiligo, epidermolysis bullosa, rosacea (long-term treating by antibiotics), blepharitis, malaria and attractiveness to mosquitoes, & skin cancer	(+) Probiotics, Prebiotics (−) Process food (emulsifiers), Gluten, some skin care and cosmetic products (may alter skin microbiome)	Ellebrecht et al. (2016), Kong et al. (2012), Maguire and Maguire (2017)
Eczema	Food allergens ➔ ↑ IgE & IgG4, IL-10, CLA positive T-cell & TNFα ➔ intestinal mucosal damage & increase intestine permeability ➔ skin reaction (erythematous rash, urticaria, & angioedema) & GI, respiratory, & cardiovascular symptoms of anaphylaxis; More children than adults	(+) Dietary restriction with allergic food (−) Common allergic food: Cow's milk, egg, wheat (gluten), soy, peanut, fish, cashew (varies with individuals)	Hauk (2010), Jaervinen et al. (2003), McAllister et al. (2019), Pike et al. (1986), Sicherer and Sampson (1999)
Psoriasis	Disturbs of the *Firmicutes*/*Bacteroidetes* Ratio ➔ microbiota dysbiosis, ➔↑ IL 1,2,6,8,12,17,23, TNFα, INF-γ, ↓SCFAs, ↑TMAO; Patients presents with positive antigliadin antibodies; Associates with metabolic syndrome, DM, Crohn's disease, ulcerative colitis, cardiovascular disease & cancer	(+) Probiotics, Fatty fish, Vitamin D (−) Western diet, Gluten, chronic consumption of alcohol	Codoñer et al. (2018), Hidalgo-Cantabrana et al. (2019), Lerner et al. (2017), Polak et al. (2021), Scher et al. (2015), Shi et al. (2020), Watanabe and Tatsuno (2017), Yu et al. (2019)
Diseases of circulatory system (cardiovascular disease – CVD)			
General	Obesity/Western diet ➔ gut dysbiosis, disrupt TJ; choline/carnitine - ↑TMA ➔ ↑gut permeability ➔ ↑LPS, activation of TLR4, signal transduction including NF-κB ➔ metabolic endotoxemia, TMAO ➔ inflammation, platelet aggregation, cholesterol-laden macrophage foam cell formation ➔ CAD Ketogenic diets ➔ ↓total cholesterol, LDL-cholesterol, triglycerides, HbA1C, & ↑HDL-cholesterol in human research; however, there were some conflicts with rodent model research	(+) Probiotics, Prebiotics, Dietary fish oil and oily fish (ω−3FAs), Ketogenic diets, Food rich in polyphenols such as resveratrol, EGCG, & curcumin, quercetin, Fruit polyphenol including berries (−) Western diet, Processed food, Gluten, Heated vegetable oil	Amar (2018), Khurana et al. (2013), Kosinski and Jornayvaz (2017), Lourida et al. (2013), Merendino et al. (2013), Miles and Calder (2012), Mitchell et al. (2015), Moludi et al. (2020), Okuyama et al. (2016), Snelson et al. (2021), Tang et al. (2019), Villa-Rodriguez et al. (2019), Watanabe and Tatsuno (2017)
Atherosclerosis	Obesity/HFD ➔ gut dysbiosis, disrupt TJ; choline/carnitine - ↑TMA ➔ ↑gut permeability ➔ ↑LPS ➔ TMAO - oxidative stress, ↑platelet reactivity & thrombus potential, macrophage foam cell activation, endothelial cell activation, plaque localization, & vascular inflammation, & ↓reverse cholesterol transport ➔ Atherosclerosis Animal-based diet ➔ ↑bile-tolerant microorganism such as *Alistipes*, *Bilophila*, *Bacteroides* & ↓*Firmicutes*	(+) Probiotics, Prebiotics, Plant-based diet (↑SCFAs), Food rich in polyphenols, EVO (-) Western diet, Processed food	Karlsson et al. (2012), Khurana et al. (2013), Miyake and Yamamoto (2013), Moludi et al. (2020), Tang et al. (2019), Woodhouse et al. (2018)
Heart failure (HF)	Disrupt gut dysbiosis & disrupt TJ; choline/carnitine - ↑TMA ➔ ↑gut permeability ➔ ↑LPS, ↑ TNFα, IL-6 & CRP ➔ TMAO - oxidative stress, ↑platelet reactivity & macrophage foam cell activation, endothelial cell activation, plaque localization, & vascular inflammation, & ↓reverse cholesterol transport oxidative stress, plaque localization, platelet activation ➔ HF, MI & stroke	(+) Probiotics, Prebiotics	Fukui (2016), Nagatomo and Tang (2015), Tang et al. (2019)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Hypertension (HTN)	HFD/high salt diets & other dietary factors ➔ disrupt gut microbiota ➔ ↑gut permeability ➔ ↑I-FABP, LPS, TH17, IL22; ↑TMA – TMAO ➔ dysfunctional sympathetic-gut communication ➔ HTN High-salt diet ➔ change gut microbiota through an effect on TH17 lymphocytes pathway EVO decrease systolic BP	(+) Mediterranean diet, High fiber food, Fruit, Oily fish, Paleolithic type diet, Low-gluten diet, Food rich in polyphenols (fruits, tea, vegetables) (-) Animal fat, Processed meat, High-salt diet, High-gluten diet, Heated vegetable oil	Amar (2018), de Punder and Pruimboom (2013), Hul et al. (2018), Jaworska et al. (2017), Kaličanin et al. (2020), Khurana et al. (2013), Kim, Ruby Goel, et al. (2018), Leong et al. (2010), Li et al. (2017), Okuyama et al. (2016), Santisteban et al. (2017), Sayon-Orea et al. (2015), Siti et al. (2019), Tang et al. (2019)
Myocardial Infarction (MI)	Obesity/high-fat diet ➔ gut dysbiosis, disrupt TJ; choline/carnitine - ↑TMA ➔ ↑gut permeability ➔ ↑LPS ➔ TMAO - oxidative stress, ↑platelet reactivity & thrombus potential, macrophage foam cell activation, endothelial cell activation, plaque localization, & vascular inflammation, & ↓reverse cholesterol transport oxidative stress, plaque localization, platelet activation ➔ Atherosclerosis ➔ MI, heart failure & stroke	(+) Probiotics, Prebiotics, Plant-based diet (↑SCFAs), Food rich in polyphenols, EVO (-) Western diet, Processed food	Carrera-Bastos et al. (2018), Khurana et al. (2013), Miyake and Yamamoto (2013), Moludi et al. (2020), Tang et al. (2019), Woodhouse et al. (2018)
Diseases of digestive system			
Acute Pancreatitis (AP)	Disruption of gut barrier & gut permeation in early stage of AP ➔ lower level of occludin and ZO-1 expression &↑inflammatory cytokines ➔ intestinal dysbiosis: ↑*Enterococcus* & ↓ Bifidobacterium ➔ infection & pancreatic necrosis ➔ systemic inflammation & complications	(+) Probiotics	Capurso et al. (2012), DeMeo et al. (2002), Fukui (2016)
Alcoholic liver disease (ALD)	Alcohol ➔ gut dysbiosis/SIBO - ↑*Escherichia coli*, *Enterobacteria*, *Alcaligenes*, *Meagsphaera*, & ↓*Lactobacillus* & *Bifidobacterium* ➔ ↑intestinal permeability ➔ LPS endotoxin and other PAMPs ➔ activate Kupffer cells ➔ ↑TNFα, IL-6, IL-1β, TLR4, MPO ➔ hepatocyte damage ➔ ↑AST & ALT ➔ ALD (through Gut-liver axis) Probiotics ➔ ↑*Lactobacillus*, *Bifidobacterium* & ↓ *Escherichia coli*, *Enterobacteria*, *Alcaligenes*, & *Actinobacteria*; ↑Claudin-1, Occludin, ZO-1, Symplerin, p130, & HIF-2α ➔ ↓intestinal permeability	(+) Probiotics, Prebiotics, Zinc, Niacin, Appropriate nutritional intake, Dietary fatty acids	Fukui (2016), Hong et al. (2019), Sung et al. (2016), Zhou and Zhong (2017)
Autoimmune hepatitis	Genetics, food antigens, food-borne pathogens & environmental cues disturb diversity of microbiota ➔ ↑plasma LPS, ↓duodenal TJ proteins ➔ imbalanced bidirectional gut-liver axis ➔ dysbiosis - ↑aerobic bacteria & ↓anaerobic bacteria ➔ autoimmunity ➔ autoimmune hepatitis Autoimmune hepatitis is associated with CD, MS, & RA	(+) Probiotics, High-fiber diet (-) Western diet, Gluten, Long time alcohol consumption (↑gram negative bacteria), Excessive food intake	Iqbal et al. (2017), Lerner et al. (2017), Lopetuso et al. (2015), McAllister et al. (2019), Plaza-Díaz et al. (2020)
Celiac Disease (CD)	90% of CD patients genetically associate with HLA DQ2/DQ8 haplotypes; tTG2 involved; CD triggered by gliadin fraction of wheat gluten & prolamines of barley & rye; Gluten releases toxic peptides in stomach ➔ ↑plasma IgA, IgG, IgM ➔ against gluten peptides, & antibodies against TG2 & EMA ➔ TJ disassembly by upregulating zonulin pathway, ➔ gut dysbiosis - ↓*Bifidobacteria*, *Firmicutes*, *Lactobacilli* & *Streptococceae* & ↑*Bacteroides*, *Bacterioidetes*, *Bacteroides fragilis*, *Prevotella*, *E. Coli*, *Proteobacteria*, *Haemophilus*, *Serratia*, *Klebsiella* ➔↑intestinal permeability ➔ gut & systemic inflammation 1% population with this gluten-induced, cell-mediated disorder; CD associates with multiple autoimmune diseases & psychological diseases such as atopic dermatitis, autoimmune hepatitis, anxiety, MS, depression, schizophrenia & panic disorder, dermatitis herpetiformis, HT, RA, Sjogren's syndrome, T1D	(+) Lifelong Gluten Free Diet – the only available treatment for CD (Allowed grains: Corn, Millet, Rice Buckwheat, Sorghum, Wild rice, Teff), Probiotics (-) Prohibited grains: Wheat, Rye, Barley, Kamut, Triticale (wheat-rye hybrid), Spelt, Oats, FODMAP diet	Cardoso-Silva et al. (2019), de Punder and Pruimboom (2013), DeMeo et al. (2002), Drago et al. (2006), Fasano (2011), Ferrari et al. (2021), Caio et al. (2020), Leffler et al. (2015), McAllister et al. (2019), Neunlist et al. (2003), Rallabhandi (2012), Severance et al. (2016), Valitutti and Fasano (2019), Weaver and Herfarth (2021)

(Continues)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Cirrhosis	Gut microbiota disrupted ➔ altering bile acid homeostasis, ↓beneficial taxa like *Lachnospiraceae*, *Bacteroidetes*, *Roseburia*, *Blautia*, & *Ruminococcaceae*, ↑*Proteobacteria*, *Fusobacterium* spp., *Veillonellaceae*, *Streptococcaceae* & ↓ SCFA ➔ dysbiosis & bacterial overgrowth ➔ disrupt TJ & ↑gut permeability ➔ release both LPS & FGF 19 (produce by bile acid bind to FXR) to portal circulation ➔ ↑proinflammatory cytokines ➔ portal hypertension & cirrhosis (through gut–liver–immune system axis & Gut–liver axis); Gut dysbiosis ➔ ↑ammonia, & ↑glutamine in astrocytes ➔ astrocyte swelling ➔ oxidative stress ➔ systemic inflammation through Gut-liver-brain axis Fructose drinks ➔↓TJ & AJ proteins ➔ ↑plasma bacterial endotoxin levels ➔ endotoxemia. Dietary choline may remove fat from hepatocytes. High-protein diet may ↑*Prevotella* & *Oscillospira*. Physical exercises can regulate intestinal permeability & improve microbiota diversity	(+) Probiotics, Prebiotics, Synbiotics, High-protein diet - egg, meat, Cruciferous vegetable (due to rich in dietary choline) (-) High fat & high-sugar diet, Unlimited fat diet, Choline-deficient diet, Alcohol ingestion, Excess fructose intake like fructose drinks	Arab et al. (2018), Cho et al. (2021), Fukui (2016), Miyake and Yamamoto (2013), Norman et al. (2012), Plaza-Díaz et al. (2020), Sharma and Singh (2016), Wang et al. (2019), Woodhouse et al. (2018)
Fatty liver disease	Poor diet habit, obesity/metabolic syndrome, type 2 DM, alcohol/drugs ➔ alteration of gut microbiota and bacteria overgrowth ➔ increase intestinal permeability ➔ ↑LPS, activation of TLR4 & TLR9 ➔ ↑Serum TNF-α, IL-1β, IL-6, CCL2, CCL5, CXCL8, & ↑ROS ➔ Oxidative stress, fibrosis, inflammation ➔ FLD (through Gut-liver axis); Oxidative stress ➔ neurodegenerative disease; LPS ➔ oxidative stress, plaque localization, platelet activation ➔ MI, CVD, peripheral artery disease	(+) Mediterranean diet, especially EVO; Probiotics, Prebiotics, Synbiotics, Vitamin E (-) Diet rich in fat, milk, dairy products, Excessive alcohol intake, Excessive fructose intake	Ferro et al. (2020), Hossen et al. (2020), Li et al. (2013), Miyake and Yamamoto (2013), Ohlsson et al. (2017), Safari and Gérard (2019), Woodhouse et al. (2018)
Inflammatory bowel disease (IBD) Types of IBD: Ulcerative Colitis (UC) Crohn's disease (Crohn's)	Genetic (some with HLA-B27 - HLA-DQ2/8 positive) & environmental factors (dietary patterns/components, malnutrition, medication & food allergy, for instance, excessive intake of FODMAP diet) ➔ SIBO ➔ ↑ intestinal permeability (↓Paneth cell antimicrobial function in Crohn's & ↓goblet cells & altered mucus function in UC) ➔ luminal changes in colon ➔ intestinal inflammation ➔ IBD Gut dysbiosis in IBD: IBD showed reduced common commensals – *Bifidobacterial* & *Bacteroides fragilis* & ↑*Proteobacteria* & *Actinobacteria*. *Yersinia* & *Pseudomonas* triggers Crohn's, & *Samonella*, *Campylobacter jejuni*, *Clostridium difficile*, *Adenovirus*, & *Mycoplasma* associated with Crohn's relapsing. *Fusobacterium varium* in colon may cause UC, & *E. coli* may maintain UC Dietary emulsifiers ➔ ↓β-diversity & cause gut dysbiosis Phytochemicals suppress pro-inflammatory cytokines like TNFα, IL-1β, IL-6 & IFN- γ. Ginger can maintain Caco-2 and HT-29/B6 cells and prevent pro-inflammatory TNFα and TJ dysfunction T-cells response to enteric bacteria ➔ ↑mucosal 5-HT & dopamine, & ↓ tissue 5-HT & NE ➔ related to CNS disorder	(+) Low FODMAP diet, Mediterranean diet, Gluten-free diet (especially for HLA-DQ2/8 positive IBD patients), Green tea, Probiotics, Prebiotics, Vitamin D, folic acid, Zinc, Glutamine, Dietary fibers (to produce SCFAs), Psyllium (↓severity of UC), Ginger (especially for Crohn's), Red wine extract (-) High FODMAP diet, Gluten (mainly HLA-DQ2/8-positive Crohn's patients), Processed food including dietary emulsifiers, Food rich in ω−6FA, NSAIDs (Crohn's), Antibiotics (Crohn's), Smoking (Crohn's)	Arrieta et al. (2009), Bancil et al. (2021), Beguin et al. (2013), Cordain et al. (2000), DeMeo et al. (2002), Fukui (2016), Guagnozzi et al. (2012), Hossen et al. (2020), Kikuchi et al. (2019), Kim, Keogh, and Clifton (2018), Lacerda et al. (2021), Li et al. (2019), Llewellyn et al. (2018), Luettig et al. (2016), Magnuson et al. (2016), Malíčková et al. (2017), McAllister et al. (2019), Michielan and D'Incà (2015), Nanayakkara et al. (2016), Neish (2009), Nunes et al. (2019), Sasson et al. (2021), Scaldaferri et al. (2013), Shin and Lim (2020), Van Buiten et al. (2018), Vazquez-Roque et al. (2013), Weaver and Herfarth (2021), Yeoh et al. (2013), Yoon et al. (2018)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Irritable Bowel Syndrome (IBS)	Genetic (some with HLA) & diet (Food triggers or aggravates 2/3 of IBS patients.) ➔ ↑serum Zonulin level ➔ ↑Serum TNF-α, IL-1β, IL-6 ➔↑epithelial permeability ➔ low-grade intestinal inflammation. IBS patients present visceral hypersensitivity due to neuronal dysfunction of ENS.	(+) Low FODMAP diet, Probiotics (-) High FODMAP diet, Gluten	Barbaro et al. (2020), Camilleri and Gorman (2007), Guagnozzi et al. (2012), Martín et al. (2022), Nanayakkara et al. (2016), Niesler et al. (2021), Rinninella, Cintoni, et al. (2019), Wu et al. (2021)
Liver steatosis	Bidirectional communication between the gut & liver through Gut–liver axis. Primary bile acid from liver & Ig A ➔ Eubiosis. Dietary habits, age, ↓physical activities, & other causes (such as NAFLD, MAFLD, ALD, drugs, food contaminants of environment origin, etc.) ➔ gut dysbiosis ➔ ↑intestinal permeability ➔ secondary bile acids metabolites ➔ portal vein ➔ filtration of damaging agents like MAMPs or PAMPs ➔ ↑ cytokines (TNFα, IL-1β, IL-6, IL-12, IL 18), chemokines (CXCL1, CXCL2, CCL2, CCL5, CCL3, CCL4), NO & ROS ➔ systemic inflammation ➔ multiple liver diseases including liver steatosis & cirrhosis. Physical exercises can modify insulin sensitivity & glucose metabolism, and ↑*Bacteriodetes*/*Firmicutes* ratio, ↑SCFAs, ↑T-reg cells ➔ improve microbiota diversity, regulate intestinal permeability & anti-inflammatory cytokines – positive effects on immune system.	(+) Probiotics, Synbiotics, Mediterranean diet, High-protein diet: egg, meat, Cruciferous vegetable (due to rich in dietary choline) (-) Western-style diet (high fat & high sugar diet), Low adherence to Mediterranean diet, High salt intake, Unlimited fat diet, Choline-deficient diet, Alcohol ingestion, Excessive fructose intake, Excessive caloric intake	Chen, Zhang, et al. (2020), Di Ciaula et al. (2020), Di Palo et al. (2020), Kim, Ruby Goel, et al. (2018), Plaza-Díaz et al. (2020), Woodhouse et al. (2018)
Necrotizing enterocolitis	LPS induces the intestinal barrier dysfunction, impaired TJ protein, ➔ activates IL-1β, IL-6, IL-8 & TNFα ➔ systemic inflammation	(-) Corn gluten meal	Bai, Gu, et al. (2019), Ling et al. (2016)
Disease of genitourinary system			
Chronic Kidney disease (CKD)	Chronic intake of Western diet including heat-treated food (leaking albumin to urine), ↓intake dietary fibers (↓potassium), prolonged GI transit time due to lacking of physical activities, dietary restrictions & comorbidities (mainly DM & CVD), change intestinal microbiota diversity (↑proteolytic microbes) ➔ gut dysbiosis, SIBO ➔ ↑intestinal permeability ➔↑ blood ammonia & uremic toxicity ➔ renal injury, fibrosis & systemic inflammation through Gut-kidney axis	(+) Dietary fiber like fruits & vegetables (for potassium), Mediterranean diet, Probiotics, Prebiotics, Low-protein diet (-) Western diet, Processed food, Gluten	Briskey et al. (2017), Fukui (2016), Hobby et al. (2019), Ondrussek-Sekac et al. (2021), Sabatino et al. (2017), Snelson et al. (2021), Yang et al. (2019)
Diseases of musculoskeletal system			
Ankylosing Spondylitis (AS)	Immunity through Gut–Joint Axis – IL-23/Th17 ➔ chronic inflammation; Oral microbiota dysfunction ➔ periodontitis; intestinal dysbiosis (↑*Lachnospiraceae*, *Prevotellaceae*, *Rikenellaceae*, *Porphyromonadaceae*, *Bacteroidaceae* & decreasing *Ruminococcaceae* families) ➔ immune response (↑total IgA) ➔ decreasing zonulin ➔ Leaky gut; 90-95% of AS patients present major risk gene - HLA-B27	(+) Dietary fish oil & oily fish, Probiotics (with fermented food), Prebiotics; Low starch intake (-) Smoking, Western diet, Gluten	Chen et al. (2015), Ciccia et al. (2014, 2017), Costello et al. (2015), de Punder and Pruimboom (2013), Fasano (2012), Obrenovich (2018), Rath et al. (1999), Tito et al. (2017), Welsby and Goriely (2016), Yang et al. (2016), Yeoh et al. (2013), Yu et al. (2015)
Muscle wasting	Gut–brain–muscle crosstalk: *Lactobacillus species pluralis* (spp.) ➔ reduce gut permeability ➔ ameliorate muscle wasting	(+) Probiotics (Fermented food like Kimchi), Prebiotics Synbiotics	van Krimpen et al. (2021)

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TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Rheumatoid Arthritis (RA)	Oral microbiota dysfunction: dental caries & periodontitis ➔ develop ACPA; Gut dysbiosis: food antigens, food-borne pathogens disturb immune homeostasis & cause T-lymphocytes/antibody reaction ➔ reducing common commensals – *Bifidobacterial* & *Bacteroides fragilis* ➔ impaired TJ ➔ systemic inflammation ➔ RA Adley (Coix lachrymal-jobi L., an annual crop) has anti-inflammatory and immunological activities, such as ↓TNFα and IL8 and intestinal TJ permeability. Legumes (Lectin) and nightshades (lectin & alkaloids) ➔↑intestinal permeability & innate immune cell activation ➔ RA symptoms.	(+) Dietary fish oil & oily fish, Probiotics, Ginger, Adley (Coix lachrymal-jobi L.) (-) Nightshades, Legumes, Western diet, Gluten	Cordain et al. (2000), Farshchi et al. (2017), Lerner et al. (2017), Lopetuso et al. (2015), Simopoulos (2008), Vojdani (2015)
Disease of respiratory system			
Asthma	Environmental allergens activate immune system – TH^2 ➔ Gut dysbiosis, ↓ratio of *Bacteroidetes/Firmicutes*, ↓Bifidobacterium, Lactobacillus, ↑*Escherichia coli*, *Streptococcus* & *Staphylococcus* ➔ ↑intestinal permeability ➔ ↑TNF & IL-6, LPS, lower expression of TLR4 ➔ inflammation through Gut–lung axis ➔ asthma Dietary fiber regulates SCFA & ↓gastric acid to protect duodenal mucosa	(+) Probiotics, Prebiotics, Synbiotics, Dietary fiber, Plant gums, Plantain family seeds (-) Allergic cascade intake, Western diet	Farshchi et al. (2017), Fasano (2012), Hijazi et al. (2004), Sahagu´n et al. (2015), Simopoulos (2008), Trivedi and Barve (2020), Trompette et al. (2014)
Endocrine or metabolic diseases			
Diabetes Mellitus (DM) Type I DM (T1D) Type II DM (T2D)	T1D: Factors influence gut microbiota composition: delivery mode - cesarean section (CS) ↑risk of childhood onset T1D than virginal delivery due to ↓ gut microbiota diversity (mainly ↓Bacteroidetes phylum) from mother; Starting cereal diet early (cDNA clones of diverse wheat storage globulins ➔ islet damage); Geographic difference: highest in Sardinia & Finland, & lowest in China & Venezuela due to genetic (HLA class II genes) & environmental effects; Immunological status; Using antibiotics – induce the proliferation of pathogen like *Clostridium difficile* & *S. enterica*; Viral infection Dietary related antigens ➔ ↑zonulin ➔ microbiota dysbiosis ➔ ↓TJ ➔↑APC ➔ ↑IgA, LPS, T cell activation ➔ PLN immune response ➔ β cell autoimmunity ➔ insulin deficiency T2D: T2D associated with visceral obesity; Lower microbial diversity ➔ dysbiosis ➔↑LPS, ↑zonulin, ↑intestinal permeability ➔ ↓saccharolytic microbes ➔↓SCFA (SCFA suppress proinflammatory mediators like TNFα, IL-1β, IL-6, & NO) ➔ endotoxemia, insulin resistance & chronical inflammation	T1D: (+) Hydrolyzed formula, Gluten-free diet or delayed introduce gluten, ω−3FAs, Probiotics (-) Early diet: Cereal, Cow milk T2D: (+) Dietary fish oil and oily fish (ω−3 FAs), Probiotics, Prebiotics, Synbiotics, Mediterranean diet, Fermented food like Kimchi, yogurt, Food rich in polyphenols like cinnamon & grapes (-) Western diet, Processed food, Gluten, Heated vegetable oil	T1D: Bekkering et al. (2013), Cardwell et al. (2008), de Kort et al. (2011), Fasano (2020), Gianchecchi and Fierabracci (2017), Li and Atkinson (2015), Petersa and Wekerle (2019), Sapone et al. (2006), Simpson et al. (2009) T2D: An et al. (2013), Bekkering et al. (2013), de Kort et al. (2011), Ejtahed et al. (2012), Fasano (2020), Jayashree et al. (2014), Lopetuso et al. (2015), Lourida et al. (2013), Merendino et al. (2013), Miles and Calder (2012), Moreno-Navarrete et al. (2012), Okuyama et al. (2016), Patra et al. (2016), Sabatino et al. (2017), Snelson et al. (2021), Watanabe and Tatsuno (2017), Zhang et al. (2014)
Hashimoto Thyroiditis (HT)	Thyroid–Gut Axis: HT, Graves' disease & thyroid carcinoma share similar mechanism, all cause dysbiosis ➔ stimulate GALT & TLR ➔ change TSH & T3 level; HPT Axis ➔ ATTA. ↓selenium & zinc ➔ decrease T4 ➔ T3; ↓iron & iodine ➔ impaired thyroid hormone synthesis. Gluten-free diet decrease thyroid antibody titers. HT related to *Hepatitis C*, *Helicobacter pylori*, *Yersinia enterolitica* & *Borrelia burgdorferi* infection HT often presents CD.	(+) Selenium, Zinc, Vitamin D, Iron, Iodine, Copper, Probiotics, Mediterranean diet, Oily fish, Gluten-free diet (-) Gluten, Processed meat	Bodinham et al. (2014), Cayres et al. (2021), Fasano (2020), Kaličanin et al. (2020), Fenneman et al. (2020), Knezevic et al. (1769), Krysiak et al. (2019))

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Metabolic endotoxemia	HFD ➔ gut dysbiosis, SIBO, ↓IAP activity, ↑CM & bile ➔ ↑intestinal permeability ➔ LPS & TLR4 ➔ ↑TNFα, IL-1β, IL-6 ➔ chronic low-grade inflammation ➔ metabolic endotoxaemia ➔ many chronic diseases such as obesity, DM, atherosclerosis	(+) Probiotics, Prebiotics, Flavonoids, ω−3FAs (-) HFD, Western diet	Kaliannan et al. (2015), Moreira et al. (2012))
Obesity	HFD, excessive gluten diet ➔ change gut microbiota, ↑*Lactobacillus*, *Staphylococcus aureus*, *Enterobacter cloacae* strain B29, ↓*Faecalibacterium prausnitzii* ➔ ↑LPS ➔ disrupt TJ & ↑gut permeability ➔ ↑TLR4 & MLCK activation, ↑release TNFα, IL-1β, IL-6, IL-8 ➔ endotoxaemia ➔ systemic inflammation ➔ obesity. Obesity associated with metabolic disorders including T2DM, insulin resistance, liver diseases and diseases in multiple systems.	(+) Food rich in polyphenols Probiotics, Prebiotics, Flavonoids (-) HFD, Gluten, Heated vegetable oil	Bekkering et al. (2013), Casselbran et al. (2015), Di Palo et al. (2020), Frazier et al. (2011), Gerard (2016), Gil-Cardoso et al. (2016), Hul et al. (2018), Kim and Ko (2018), Guercio Nuzio et al. (2017), Okuyama et al. (2016), Shi et al. (2021), Silva et al. (2020), Stenman et al. (2016), Zak-Gołąb et al. (2013))
Immune disease			
Systemic Lupus Erythematosus (SLE)	Dysbiosis in gut microbiome (↓*Firmicutes*/*Bacteroidetes* ratio) ➔ Leaky Gut ➔ ↑ LPS (↑soluble CD 14) & proinflammatory cytokines (IL17, IL 21-23 & IFNα) ➔ systematic inflammation, cell apoptosis, anti-dsDNA Ig production; Fc gamma receptor IIb dysfunction ➔ ↓immune response; Related to RA, T1D, MS, & IBD	(+) Dietary fish oil and oily fish (ω−3FAs), Probiotics, Prebiotics (-) Western diet, Nightshades	Abdelhamid and Luo (2018), Lopetuso et al. (2015), Mu et al. (2017), Thim-uam et al. (2020), van der Meulen et al. (2016), Watanabe and Tatsuno (2017)
Neoplasms			
General	Disruption of microbiota ➔ gut dysbiosis ➔ MAMPS ➔ ↑ LPS, activate TLRs, & release proinflammatory cytokines ➔ carcinogenesis Bacteria associated with carcinogenesis such as *Helicobacter pylori*, *Fusobacterium nucleatum*, *Streptococcus gallolyticus*, *Bacteroides fragilis*, *Salmonella typhi*, *Chlamydia pneumonia*, *Mycoplasma* sp., *Prevotella* sp., *Bacillus* sp. ➔ genotoxicity, release of ROS, RNS ➔ carcinogenesis Very low-carbohydrate ketogenic diets ➔ ↓serum glucose & insulin growth factor ➔ delay cancer progression Intestinal mucosa release SCFAs to protect carcinogens. Glutenous diets ➔ ↑risk of lymphoma (usually non-Hodgkin's lymphoma) due to associate with CD especially silent & latent CD	(+) Probiotics, Prebiotics, Mediterranean diet, Vegetarian diet, Japanese diet, very low-carbohydrate Ketogenic diets, Dietary fish oil and oily fish (ω−3FAs), Dietary phytochemicals, Resveratrol, Vitamins, Essential minerals (-) Western diet, Processed food, Gluten	de Punder and Pruimboom (2013), Ferrari et al. (2021), Hoggan (1997), Klein et al. (2012), Laura Soldati et al. (2018), Merendino et al. (2013), Miles and Calder (2012), Raza et al. (2019), Shabbir et al. (2021), Snelson et al. (2021), Watanabe and Tatsuno (2017)
Gliomas	↑zonulin expression ➔ altered gut TJ ➔ altered BBB ➔ glioma C6 conditioned media - ↑HGF, VEGF, zonulin, PGE2, & ↓EGF ➔ IL-1β, IL-6, IL-8, TNFα, CXL13 ➔ gliomas	(+) Ketogenic diet (-) High-calorie diet	Díaz-Coránguez et al. (2013), Jonathan et al. (2020), Skardelly et al. (2009))

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TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Neurological and psychological diseases			
General	Leaky gut ➔ leaky brain: through MGB axis, GBNM axis, HPA axis & multiple pathways like neuroendocrine immune, ANS, & ENS. The BBB includes endothelial cells, TJ, pericytes, basement membrane & astrocyte end-feet ensheathing the capillary wall. Brain presents similar junctional proteins as gut TJ proteins. Gastro-intestinal-derived hormonal secretion, commensal bacteria produce neurotransmitters & neuromodulators: *Lactobacillus*, *Bifidobacterium* (produces GABA), *Escherichia*, *Bacillus* & *Saccharomyces* (produces NE), *Bacillus* (produces dopamine), *Lactobacillus* (produces acetylcholine), *Candida*, *Streptococcus*, *Escheridia*, *Enterococcus* spp. (produces serotonin) & *Lactobacillus plantarum* (may stimulate BDNF). Gut bacterial composition manipulates behavior. Dysbiosis ➔ altering TJ at BBB ➔ dysregulation of MGB axis ➔ dysfunction of GABA, serotonin & BDNF ➔ releasing pro-inflammatory cytokine: IL-1, IL-6, IL-18 (bacterial cell wall LPS induced), TNF, IFN; inhibiting IL-10, IL-12, IL-15 & T-cells; & chemically related to 5HT, 5HIAA, & HVA ➔ effect on brain & behavior. Chronic stresses in adult effects gut microbiota ➔ IL-1 & IL-6 & ↑cortisol release through HPA axis. Stress ↓gluten tolerance ➔ "hyper-excitable celiac brain". Dietary aquaporin (corn, soybean, spinach leaf, tomato aquaporins) may cross-react with brain astrocytic endfeet ➔ broken BBB ➔ neuroautoimmunity ➔ neurological disorders. Dietary fiber produces SCFAs. SCFAs – the key signaling metabolite (Eubiosis) – regulate & maintain the BBB.	(+) Probiotics, Prebiotics, Ketogenic diet, Yogurt, Dietary fiber (produces SCFA) (-) Gluten (for some diseases); Antibiotic use; Western diet; Dietary aquaporins - corn, soybean, spinach leaf, tomato aquaporins (related to demyelinating diseases, Gluten ataxia, Guillain Barre syndrome, Miller Fisher syndrome, MS, motor neuron disease, myasthenia gravis, etc.)	Braniste et al. (2014), Cryan et al. (2020), Dinan and Cryan (2017), Galland (2014), Kuwahara et al. (2020), Lambert et al. (2018), Mittal et al. (2017), Obrenovich (2018), Osadchiy et al. (2019), Rahman et al. (2018), Rea et al. (2020), Rieder et al. (2017), Rutsch et al. (2020), Seguella et al. (2019), Slyepchenko et al. (2017)
Aging	Human keeps stable & diversity of gut microbiota till 40 years. Changing diet, using antibiotics & medications, ↓exercises, & ↑stress ➔ ↓ microbiota diversity ➔ low grade, chronic inflammation, ↑IL-6 & TNF with changing *Bacteroidaceae* & *Erysipelotrichaeae*; thinner mucus & ↓mucin with changing *Clostidiaceae*, *Akkermansiaceae*, *Bifidobacteriaceae*, & *Bacteroidaceae*; ↓immune tolerance/immune senescence with changing *Clostidiaceae*, *Bifidobacteriaceae*, *Lachnospiraceae*, & *Coriobacteriaceae*; & ↓ SCFA ➔ aging & frailty. Bland food ➔ ↓microbiota diversity. If ↑ microbiota diversity ➔ less aging.	(+) Probiotics, Prebiotics, Mediterranean diet, High-fiber diet, Food rich in polyphenols such as resveratrol, EGCG, curcumin & quercetin (-) Bland & low-fiber food (often in nursing homes), Antibiotics & medications, High saturation fat diet, High-sugar diet	Cryan et al. (2020), DeJong et al. (2020), Khurana et al. (2013)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Alzheimer's disease (AD)	AD is the most common form of dementia. Aging ➔ ↓microbial diversity & naïve T cells ➔ ↑risk of AD. Obesity, HTN & T2DM also disrupt gut & BBB permeability ➔ ↑risk of AD. APOE gene – risk of AD APOE gene, aging & unbalanced diet ➔ ↑*Verrucomicrobia*, *Escerchia/Shigella*, *Proteobacteria*, & *Pseudomonas aeruginosa*, & ↓*Eubacterium hallii*, *Bacillus fragilis*, *Bacteroides fragilis*, *Eubacterium rectale*, & *Faecalibacterium prausnitzii* ➔ disturb intestinal permeability & BBB permeability through MGB axis, communicating with vagal & spinal nerve & HPA axis ➔ dysbiosis of microbiota (gut, mouth, nose) ➔ ↑ secretion of β-amyloid (Aβ) & LPS ➔ ↑IL-1β, IL-6, IL-18, TNFα & IFN-γ in neurons, microglia, & astrocytes; imbalance of GABA, serotonin, histamine, & dopamine, &↓SCFA ➔ Aβ plaques & neurofibrillary tangles ➔ neuroinflammation, cognitive deficits & neurodegeneration ➔ AD Western diet ➔ ↑*Flavobacterium*, *Runella*, & *Flectobacillus* ➔ ↑ IL-1β & NF-κB ➔ disrupt GB axis ➔ inflammation AD patients showed ↓melatonin level. Using melatonin may prevent AD or slow down AD progression	(+) Mediterranean diet, Ketogenic diet, Probiotics, Prebiotics, Vitamins (B compound), ω−3FAs, High fiber diet, Polyphenol - high consumption of vegetables & fruits, Antioxidants, Melatonin (-) Western diet, Antibiotics, Dietary aquaporin	De-Paula et al. (2018), Fan et al. (2019), Fox et al. (2019), Kesika et al. (2021), Khurana et al. (2013), La Rosa et al. (2018), Lambert et al. (2018), Liu et al. (2020), Lourida et al. (2013), Megur et al. (2020), Moreno-Navarrete et al. (2012), Obrenovich (2018), Rutsch et al. (2020), Saji et al. (2020), Shabbir et al. (2021), Sochocka et al. (2019), Vogt et al. (2017)
Amyotrophic Lateral Sclerosis (ALS)	Through MGB axis: intrinsic or extrinsic factors ➔ change gut microbiota diversity ➔ disturbance of TJ proteins & intestinal barrier ➔ ↑LPS, ↑IL-1β, IL-6, TNFα, IFN-γ ➔ Disruption of BBB & BSCB (endothelial cells, TJ, pericytes, basal lamina & astrocytic foot processes) ➔ neuropathy of ENS (multi-functional RNA-binding protein TDP43 linking between ENS & CNS) ➔ ↓GABA, glial cell loss, proteostasis-associated defects, glutamate excitotoxicity; dysfunction of mitochondrial, oxidative stress, SOD-1, TCP-43, C9orf72, jettisoned, organelles; cytoskeletal, axonal, & transport vesicle defects ➔ ALS Use Probiotics - "BUGS as DRUGs" (Obrenovich et al., 2020) for neurodegenerative diseases including ALS	(+) Probiotics, Prebiotics, Symbiotics, Polyphenols, Flavonoids, Caffeine	Blacher et al. (2019), Fang (2018), Niesler et al. (2021), Obrenovich (2018), Obrenovich et al. (2020)
Anorexia nervosa (AN)	Poor diet or insufficient food intake like protein-deficient diet, plus stress ➔ alter gut-brain interaction through MGB axis, HPA axis, & vagus nerve ➔ gut dysbiosis ➔ ↓SCFA, serotonin, & BDNF at hippocampus area & ↑cortisol & cytokines ➔ neuroinflammation, cognitive dysfunction & mood changes. AN associate with Crohn's disease & IBS.	(+) Probiotics, Prebiotics, Vitamins & minerals, Diet with high fiber & low saturated fat (-) Western diet, Processed food	Herpertz-Dahlmann et al. (2017)
Anxiety disorder	Gut dysbiosis plus chronic stress through MGB axis ➔ ↓SCFA-producing bacteria & ↑*Escherichia-Shigella*, *Fusobacterium*, & *Ruminococcus gnavus* ➔ Brain chemical imbalance (↓serotonin, GABA & dopamine & ↑cortisol & NE), glia abnormalities ➔ central & peripheral persistent low-grade immune inflammation through HPA axis & ANS ➔Anxiety. Anxiety related to IBD, CD. Fermented food ↑ SCFAs, GABA, & ↓LPS, IL-1β, IL-6, TNFα, & NF-κB and improve TJ and gut barrier function.	(+) Vitamin B2, 3, 6, & 12; Probiotics, Prebiotics, Fermented food (-) Gluten, HFD	Aslam et al. (2020), Dinan and Cryan (2017), Jianga et al. (2018), McAllister et al. (2019), Plaza-Díaz et al. (2020), Rudzki and Maes (2020)

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TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Attention deficit hyperactivity disorder (ADHD)	Genetic, epigenetic, & dietary factors ➔ imbalanced gut microbiomes, ↑*Bacteroides uniformis*, *Bacteroides ovatus*, & *Sutterella stercoricanis* ➔ ↑zonulin ➔ ↑permeability in GI system & BBB through MGB axis ➔ glia abnormalities ➔ ADHD (inattention, hyperactivity, impulsivity & impairment of social function) Comorbidity with ASD	(+) Probiotics, Prebiotics, Synbiotics, Vitamins (-) High fat intake, High sugar intake, High refined grains intake, Antibiotics	Chou et al. (2018), Wang et al. (2020), Özyurt et al. (2018), Partty et al. (2015), Proctor et al. (2017), Rudzki and Maes (2020)
Autism spectrum disorder (ASD)	Prenatal stress (maternal infection, inflammation & antibiotics, & maternal high fat diet), diet ➔ ↓gut microbiota diversity, alter microbiota, ↑*Firmicutes/Bacteroidetes* ratio, ↑*Acidobacteria*, *Enterobacteriaceae*, *Pseudomonadaceae*, *Veillonellaceae*, & *Megamonas*; ↑*Lactobacillus* spp. & *Desulfovibrio* spp., & ↑GI *Candida albicans* ➔ ↑zonulin & LPS ➔ ↑permeability in GI system & disrupt BBB through MGB axis, HPA axis, ANS (vagus nerve) ➔ ↑IL-6, IL-1β, IL-8, TNFα & IFN-γ; alteration of serotonin, GABA, dopamine, glutamate, SCFAs & Treg cells; accumulation of AGEs in the brain through AGE-RAGE axis ➔ ASD. Ketogenic diet regulates mitochondrial function & improve mood balance of the brain, but may have adverse effects, such as constipation, hypercholesterolemia, etc. Gluten- and casein-free diet – prevent immune response to gluten (antibodies against gluten in ASD is different with celiac disease) & casein, & ↓urinary peptide and improve behavior. ASD related to IBD (UC & Crohn's Disease).	(+) Ketogenic diet, Probiotics, Prebiotics, Mother's milk (↑SCFA), Gluten & casein-free diet (-) Gluten, Casein (cow & goat's milk, ice cream, butter & cheese), Gluten, Dietary aquaporin	Esnafoglu et al. (2017), Fattorusso et al. (2019), Fowlie et al. (2018), Galland (2014), Hughes et al. (2018), Józefczuk et al. (2018), Karakuła-Juchnowicz et al. (2017), Lambert et al. (2018), Mayer et al. (2014), Obrenovich (2018), Özyurt et al. (2018), Tagliabue et al. (2017)
Bipolar disorder (BD)	Through Gut–brain axis: Stress & other factors ➔ ↑IgM/IgA response to LPS & other Gram-negative bacteria ➔ gut dysbiosis ➔ intestinal permeability ➔ ↑proinflammatory cytokines: IL-2, IL-6, IL-1β, TNFα & ↓anti-inflammatory cytokines: IL-4 ➔ disrupt TJ protein of BBB ➔ ↑BBB permeability ➔ imbalance of neurotransmitters: 5-HT, tryptophan, kynurenine, picolinic acid, quinolinic acid ➔ immune system dysfunction ➔ BD. BD is associated with metabolic & cardiovascular diseases	(+) Probiotics (-) Smoking	Chen, Park, et al. (2020), Doney et al. (2021), Painold et al. (2019), Simeonova et al. (2020)
Dementia	Change in microbiota ➔↑Enterotype I & III bacteria & ↑serum triglyceride & serum C-reactive protein, ↓*Clostridia* & its phylum Firmicutes & ↓SCFAs & indole-3-pyruvic acid ➔ gut dysbiosis & disrupt BBB through MGB axis cause glia abnormalities ➔ ↓memory, & other cognitive deficits	(+) Mediterranean diet, Low fat diet with calorie restriction, ω−3FAs (-) Western diet with high fat & sugar, Gluten, Alcohol	Wang et al. (2020), Lourida et al. (2013), Merendino et al. (2013), Obrenovich (2018), Rudzki and Maes (2020), Shabbir et al. (2021), Watanabe and Tatsuno (2017)
Epilepsy	Through MGB axis or GMB axis: Genetic & environmental factors ➔ disrupt gut microbiota diversity ➔ disrupt TJ protein ZO-1, claudin-5, & occludin ➔ TJ disassembly ➔ ↑ intestinal permeability ➔ ↑IL-17A, IL6, IL1β, IFN-γ ➔ breakdown BBB ➔ Epilepsy Approximately 1/3 patients with epilepsy have drug resistance. Ketogenic diet is used for drug resistant epileptic patients. After Ketogenic diet therapy, epilepsy patients showed ↑ in gut *Bacteroidetes*, *Actinobacteria* phylum & ↓*Proteobacteria* Genetic disorder - GLUT1 DS often associates with epilepsy	(+) Ketogenic diet, Probiotics, Prebiotics, Vitamins, Minerals	Arulsamy et al. (2020), Dahlin and Prast-Nielsen (2019), Fan et al. (2019), Rahman et al. (2018), Rinninella, Cintoni, et al. (2019)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Major depressive disorder (MDD)	Food antigens plus physiological & psychological stress ➔ altered microbiota (such as ↑*Actinomycineae*, *Coriobacterineae*, *Lactobacillaceae*, *Streptococcaceae*, *Clostridiales*, *Eubacteriaceae*, *Lachnospiraceae*, *Ruminococcaceae*, *Erysipelotrichaceae*; ↓*Bacteroidaceae*, *Rikenellaceae*, *Lachnospiraceae*, *Acidaminococcaceae*, *Veillonellaceae*, *Sutterellaceae*) through MGB axis, more specifically MGIG axis. Dysbiosis, SIBO, parasitic & fungal infection ➔ ↑BBB permeability & autoimmunity ➔ ↑TNFα, IL-1β, IL-6, IFN-γ, NF-κB, O&NS, & hsCRP, ↓IL-4, also ↑ serum IgA & IgM to LPS of G- enterobacteria, ↑I-FABP ➔ brain chemical imbalance: ↓serotonin, NE, dopamine, GABA, BDNF & ↑cortisol ➔ glia abnormalities ➔ central & peripheral persistent low-grade immune inflammation through HPA axis & ANS ➔ MDD; Gluten sensitivity ➔ ↑ serum IgG ➔ effect to MDD; HFD ➔ ↑the ratio of *Firmicutes to Bacteroidetes* & *Proteobacteria* (G- LPS contained bacteria); Fermented foods can increase lactic acid bacteria such as *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, *Bifidobacterium*, & *Leuconostoc* and ↑SCFAs, GABA, & ↓LPS, IL-1β, IL-6, TNFα, & NF-κB, improve gut barrier function and anti-inflammation. MDD is associated with IBS, obesity, T2DM & chronic fatigue syndrome, & they share similar mechanisms.	(+) Mediterranean diet, Low fat diet with calorie restriction, Cabbage (AHR ligands – anti-inflammatory properties), Probiotics, Prebiotics, Fermented foods, Vitamin B2, 3, 6, & 12 (-) Western diet with high fat & sugar, Gluten, Alcohol, Pesticides, Drugs (NSAIDs, antibiotics)	Alvarez-Mon et al. (2019), Aslam et al. (2020), de Punder and Pruimboom (2013), Doney et al. (2021), Fukui (2016), Fung et al. (2017), Karakuła-Juchnowicz et al. (2017), Liśkiewicz et al. (2021), McAllister et al. (2019), Obrenovich (2018), Plaza-Díaz et al. (2020), Rudzki and Maes (2020), Slyepchenko et al. (2017)
Migraine headache (MH)	Disrupt gut microbiota ➔ ↑intestinal permeability, ↑LPS, IL-1β, IL-6, TNFα, & ↓SCFA, ↓5-HT & serotonin ➔ BBB dysfunction ➔ inflammation through gut–brain axis ➔ may act on trigeminovascular system ➔ MH Food allergy ➔ ↑ serum IgG ➔ MH MH is associated with CD, IBD, anxiety & depression.	(+) Probiotics, prebiotics, Ketogenic diet, Ginger (-) Food allergy	Dai et al. (2017), Fan et al. (2019), Karakuła-Juchnowicz et al. (2017), Luettig et al. (2016), Nouri et al. (2014), Parohan et al. (2020), Roos et al. (2017)
Multiple Sclerosis (MS)	Through gut–brain axis & HPA axis: one of the factors is dietary factor (mainly Western diet) ➔ ↑lactulose/mannitol ratio, disturb commensal gut microbiota (such as ↑*Methanobrevibacter*, *Akkermansia*; ↓*Butyricimonas*) ➔↑serum zonulin ➔ Gut dysbiosis ➔ ↓Treg/Th17 ratio at intestinal mucosa, ↑LPS - damage intestinal barrier ➔ NF-κB & AP-1 ➔ exdotoxemia & ↑TNFα, IFN-γ, IL1β, 2, 6, 18, hs-CRP, RANKL, ROS ➔ gut inflammation (similar to IBD) & chronic systemic inflammation ➔ breakdown BBB ➔ damage nerve fibers and myelin sheath at brain, spinal cord & optical nerve. Hypercaloric diets ➔ postprandial inflammation; Antigens ➔ ↓ SCFAs; Food contains lectin & alkaloids may influence nerve, brain, muscle & GI function negatively. Two special diets for MS: 1. Swank Diet: A low-fat diet eliminated all red meat and dairy; 2. Wahls Elimination Diet: modified Paleo diet, exclude all grains, dairy, legumes & nightshades and emphasized fruits and vegetables, meat and fish.	(+) Two special diets for MS: 1. Swank Diet, 2. Wahls Elimination Diet; Mediterranean Diet (Gluten limits to whole grain); Ketogenic diet, Probiotics; Vegetables, Seafood & fish oil; Seaweed & Algae; Fermented food; Multivitamins/minerals (-) Western diet; Nightshades; Gluten; Cow's milk (bovine milk casein); Sweeteners; Dietary aquaporins; Smoking	Berer et al. (2017), Buscarinu et al. (2018, 2019), Camara-Lemarroy et al. (2018, 2020), Cantarel et al. (2015), Chen et al. (2018), Chu et al. (2018), de Punder and Pruimboom (2013), Esposito et al. (2018), Jangi et al. (2016), Lambert et al. (2018), Lerner et al. (2017), Lopetuso et al. (2015), Norman et al. (2012), Nouri et al. (2014), Ochoa-Repáraz et al. (2018), Pellizoni et al. (2021), Rahman et al. (2018), Raza et al. (2019), Reynders et al. (2020), Riccio and Rossano (2015), Rutsch et al. (2020), Shahi et al. (2017), Wahls et al. (2019)

(Continues)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Parkinson's Disease (PD)	Unbalanced nutrition, aging, ↑ toxins, infection, & use of antibiotics ➔ microbiota dysbiosis (such as ↑*Blautia*, *Coprococcus*, *Roseburia*, *Proteobacteria*; ↓*Faecalibacterium*, *Prevotellaceae*) ↓SCFA, ↑LPS, & accumulation of α-syn in ENS (↑oxidative stress & localized inflammation) ➔ ↑gut permeability & BBB permeability ➔ ↑enteric glial-related proinflammatory markers such as GFAP, Sox-10, IL-6, IL-1β, TNFα ➔ bidirectional communication between the brain & gut through gut–brain axis, MGB axis, GBNM axis, ENS, Vagus nerve & innate immunity (via TLR signaling) ➔ accumulation of α-syn & Lewy bodies in CNS & widespread in other nervous systems ➔ neurodegeneration & neuroinflammation ➔ PD Antibiotic use is still a controversial topic for PD patients in research articles (e.g., using antibiotics is a negative effect for microbiota; Koutzoumis et al., 2020), but antibiotics such as Rifaximin is effective to treat SIBO (Aho et al., 2021)	(+) Mediterranean diet, Ketogenic diet, Food contains PUFA, ω−3FA, High fiber diet, Probiotics, Prebiotics, Synbiotics (such as fermented milk), Polyphenol - high consumption of vegetables & fruits, Caffeine (-) Western diet (high intake of animal protein, saturated fat, refined grain, sugar, alcohol, high salt diet, high fructose corn syrup & low intake of fruits & vegetables)	Aho et al. (2021), Cryan et al. (2020), Fan et al. (2019), Fang (2018), Fung et al. (2017), Gatta and Scarpignato (2017), Koutzoumis et al. (2020), O'Donovan et al. (2019), Obrenovich (2018), Rutsch et al. (2020), Uyar and Yildiran (2019)
Schizophrenia	Multiple risk factors such as infection, inflammation, antibiotics use, stress, toxins, genes (HLA), food antigens ➔ breakdown TJ, AJ, & BBB ➔ ↑intestinal & BBB permeability through gut-brain axis ➔ ↑C1q, cytokines, MHC, pentraxin, sCD14, TLRs ➔ autoimmunity & glia abnormalities ➔ Schizophrenia Schizophrenia presents a non-celiac IgG sensitivity. tTG & deamidation modify toxic peptides from broken-down gluten proteins may be attacked by T-cell immune response. Schizophrenia is associated with CD, metabolic & cardiovascular diseases.	(+) Gluten & casein-free diet, Probiotics, Prebiotics, High in fruits, vegetable & fiber (-) Gluten, Bovine milk casein, Western diet, Smoking	Barber et al. (2019), McAllister et al. (2019), Rudzki and Maes (2020), Severance et al. (2016), Simeonova et al. (2020), Turner (2009), Wahls et al. (2019))
Stroke	Disruption of microbiota diversity, ↑*proteobacteria* & ↓*Bacteroides*, *Prevotella*, & *Faecalibaterium*, ↓blood trimethylamine N-oxide ➔ disrupt TJ protein ZO-1, claudin-5, & occludin ➔ TJ disassembly ➔ ↑ intestinal permeability & breakdown BBB ➔ ↑D-Lactate & IFABP (markers of intestinal barrier integrity); ↑IL-17A, IL-17 γδ T cells, IFN-γ & TMA ➔ TMAO ➔ ischemic stroke After stroke ➔ ↑gut permeability ➔ systemic inflammation	(+) Mediterranean diet, ACN rich diet or ACN supplements (-) Western diet (red meat, processed meat & saturated fat)	Camara-Lemarroy et al. (2021), Cryan et al. (2020), Lourida et al. (2013), Manolescu et al. (2019), Psaltopoulou et al. (2013), Rahman et al. (2018), Tang et al. (2019)
Ophthalmological diseases			
Age related macular degeneration (AMD)	The pathogenesis is through gut–retina axis. Western diet interrupts *ecosystem*. Reduce gut microbiota – mainly *Bacteroidetes* & *Firmicutes* ➔ ↓TJ protein – ZO1 & Occludin ➔ ↑ intestinal permeability ➔ low-grade chronic systemic inflammation	(+) ω−3FAs rich food: dietary fish oil and oily fish, wild plants, eggs, nuts, & berries; Low fat, Low glucose/fructose diet; Vitamin C, E, D, Zinc, β-carotene, Lutein, Zeaxanthin (-) Western diet, Smoking	Fasano (2012), Merendino et al. (2013), Miles and Calder (2012), Rinninella et al. (2018), Schleicher et al. (2013), Simopoulos (2008), Watanabe and Tatsuno (2017)

TABLE 1 (Continued)

Diseases	Basic mechanism	Potential dietary components/ Supplements that influence diseases	References
Dry eye syndrome	Similar as AMD. Increased inflammatory cytokines (IL-1, IL-6, & TNFα) in tears	Similar as AMD	Simopoulos (2008), Solomon et al. (2001)

Abbreviations: (-), Negative effect/Risk factors; (+), Positive effect/beneficial factors; 5HIAA, 5-hydroxyindoleacetic acid; 5HT, 5-hydroxytryptamine; ACN, anthocyanin; ACPA, anti-citrullinated protein antibodies; ADEs, advanced glycation end products; AHR, aryl hydrocarbon receptor; ALD, alcoholic liver disease; ANS autonomic system; AP-1, Activator Protein-1; APC, antigen-presenting cell; ATTA, anti-tissue transglutaminase antibodies; BBB, blood brain barrier; BDNF, brain derived neurotrophic factor; BSCB, brain-spinal cord barrier; C1q, complement component 1q; CLA, cutaneous lymphocyte antigen; CM, chylomicrons; CRP, C-reactive protein; EGF, epidermal growth factor; FGF 19, fibroblast growth factor 19; FXR, farnesoid X receptor; GABA, gamma-aminobutyric acid; GALT, gut-associated lymphatic tissue; GBNM, gut–brain neuroendocrine metabolic; GLUT1 DS, Glucose Transporter 1 Deficiency Syndrome; HGF, hepatocyte growth factor; HLA, human leukocyte antigen; hs-CRP, high-sensitivity C-reactive protein; HVA, homovanillic acid; IAP, intestinal alkaline phosphatase; IFABP, intestinal fatty acid-binding protein; LBP, LPS-binding protein; MAFLD, metabolic-dysfunction-associated fatty liver disease; MAMPs, microbial-associated molecular patterns; MGB, microbiota-gut-brain; MHC, major histocompatibility complex; NE, norepinephrine; O&NS, oxidative and nitrosative stress; PLN, perihepatic lymph node; RAGE, Receptors for AGEs; RANKL, receptor activator of nuclear factor kappa beta; ROS, reactive oxygen species; sCD, soluble cluster of differentiation; spp, plural of species; Th, T helper cell; TMAO, proatherogenic trimethylamine-N-oxide; TSH, thyroid-stimulating hormone; tTG, tissue Transglutaminase; tTG2, Auto-antigen-tissue transglutaminase 2; VEGF, vascular endothelial growth factor; α-syn, alpha-synucleinopathy.

(Okuyama et al., 2016; Sayon-Orea et al., 2015). Food antigens such as bovine milk proteins and collagen, egg allergen, and wheat gluten cause food sensitivities that lead to intestinal and systemic inflammation through IgA, IgE, IgG-mediated transport (Li et al., 1999; Ma et al., 2021; Ménard et al., 2010; Severance et al., 2016).

5 | POTENTIAL MECHANISMS OF DISEASES RELATED TO GUT FUNCTION AND DIETARY INFLUENCES

The goal of this review was to synthesize the current literature related to gut barrier dysfunction, associated diseases, and food influences. We summarized related diseases, possible mechanism, and dietary influences in the table below. The disease classifications are based on the International Classification of Disease, Eleventh Revision (ICD-11). Dietary influences are the most important factor to gut microbiota. However, fecal microbiota transplantation has been reported to be effective to most of diseases due to modification of gut microbiota. It is not included below as this table is mainly concerned with dietary intervention (Table 1).

6 | CONCLUSIONS

Based upon the current literature, there is strong evidence that dietary changes might offer therapeutic strategies to address gut barrier dysfunction. Research is underway to study and examine the relationship between food, gut function, and disease management. Nevertheless, "leaky gut syndrome" is not completely substantiated and there are still conflicts in multiple areas. However, the identification of offending foods can play an important role in the prevention and mitigation of different conditions. Personalized abstaining from harmful food and diet may prevent and treat multiple diseases. Diet could be a controllable lifestyle choice in both positive and negative effects. Diet management could be future personalized medicine.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current review.

ORCID

Linda Liang https://orcid.org/0000-0002-8314-766X

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