Dietary phytochemicals modulate intestinal epithelial barrier dysfunction and autoimmune diseases

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Abstract
The intestinal epithelium acts as a key defensive barrier that protects internal organs from the detrimental gut environment. The homeostasis of the gut epithelium may be altered by environmental conditions and exogenous pathogens that can impair the integrity of the gut barrier, leading to immune response associated with low-grade systemic inflammation, a known contributor to metabolic and inflammatory diseases. Autoimmune diseases (ADs) are a collection of abnormalities of the immune system, in which the immune system of an individual acts against healthy organs or systems, due to a failure in antigenic recognition. Hence, this review aims to focus on modulators of intestinal epithelial barrier dysfunction with effects on autoimmune disorders. All data on dietary phytochemicals and their impact on the modulation of the intestinal epithelium barrier and various ADs were collected from electronic searches of library databases (PubMed, Science Direct, and Google Scholar). An electronic search was conducted using PubMed, Science Direct, and Google Scholar by finding the keywords “phytochemicals” AND “bioactive compounds” AND “flavonoids” AND “polyphenols” OR “intestinal epithelium barrier” OR “autoimmune diseases” OR “inflammatory diseases” in “Title/Abstract/Keywords,” with the date from January 2011 to December 2020, to identify all published studies (in vitro, in vivo, clinical, and case-control) that have investigated the connection between dietary phytochemicals and their various beneficial effects. Dietary phytochemicals are promising key modulators, stabilizing the integrity of the intestinal barrier and attenuating the progression of ADs. Health-modulatory information was gathered and orchestrated in a suitable place in this review.

KEYWORDS
autoimmune diseases, dietary phytochemicals, inflammation, intestinal epithelial barrier, modulatory effects

Abbreviations: AD, autoimmune disease; AJ, adherens junctions; AJC, apical junction complex; Akt, serine/threonine-specific protein kinase; ALS, amyotrophic lateral sclerosis; B cells, bone marrow cells; CAT, catalase; CD, cluster of differentiation; CD4+, cluster of differentiation 4+; EGCG, epigallocatechin-3-gallate; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase 1; IBD, inflammatory bowel disease; IFN-γ, interferon-gamma; IL, interleukin; MAPK, mitogen-activated protein kinase; MLCK, myosin light-chain kinase; MUC2, mucin 2; NO, nitric oxide; NF2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SOD, superoxide dismutase; Src, signet ring cell; T cells, thymus cells; TFEB, transcription factor EB; Th, T helper cells; T1DM, type 1 diabetes mellitus; TJ, tight junctions; TMAO, trimethylamine-N-oxide; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis
INTRODUCTION

Over the last decades, numerous studies have been conducted to investigate the crucial functions of the gut and its contents in human health and the progression of various diseases. The gut is a complex anatomical organ, consisting of mucosae involved in the digestion and absorption of major nutrients with water, representing the main interface between the human body and the outside environment (Bernardi et al., 2019). It includes a huge number of specialized immune cells that are involved in the defensive responses, where the epithelial surface of the gut is repetitively exposed to dietary antigens (Ganesan et al., 2018). Similarly, the mucosa of the intestinal tract also participates in the defense mechanism to prevent the entry of microorganisms and dietary antigens (Peron et al., 2019).

This permeability of this gut barrier is often controlled by dynamic functions for the concurrent fulfillment of the nutrient absorption and defense mechanisms. The small number of nutritional antigens and microorganisms do frequently enter the gut without any pathogenic stimuli. This event habitually produces a homeostatic immune response considered to be an immune tolerance to exogenous antigens (Kumar Singh et al., 2019). Furthermore, increased gut paracellular permeability facilitates an increased pervasion of luminal antigens, which will eventually cause damage to the intestinal barrier. These processes in turn activate the mucosal immune system, ultimately leading to sustained inflammation and gut damage (Karl et al., 2017).

Gut permeability is a dynamic mechanism, regulated by various factors in the host, such as intake of nutrients, microbiota, immune cells, and barrier constituents. Changes in these functions of the mucosal barrier are highly connected to a broad spectrum of various pathologies such as intestinal disorders, including inflammatory bowel disease (IBD) (Ganesan, Jayachandran et al., 2020; Garcia-Carbonell et al., 2019; Schoultz & Keita, 2019), celiac diseases (Freire et al., 2019; Rinninella et al., 2019), irritable bowel syndrome (Oshima & Miwa, 2016), metabolic syndrome (Festi et al., 2014; Ganesan et al., 2018; Ganesan, Ramkumar et al., 2020), neurological disorders (Dempsey et al., 2019; Fornai et al., 2018), autoimmune diseases (ADs) (Camara-Lemarroy et al., 2018), liver diseases (Fukui, 2019), kidney diseases (Meijers et al., 2018), and cancers (Bhat et al., 2019; Ganesan & Xu, 2020; Jin et al., 2018). Disturbance of mucosal barrier function is an early event likely preceding the onset or reappearance of inflammatory diseases. This failure or damage to the functions of the mucosal barrier is generally referred to as “Leaky gut syndrome.” Therefore, the gut luminal mucosal epithelium acts as a structural and immunological barrier against the broad spectrum of noxious substances and exogenous antigens. The regulation of function of the gut mucosal barrier is significant in sustaining gastrointestinal mucosal homeostasis.

ORGANIZATION OF INTESTINAL EPITHELIAL BARRIER

The gut mucosa is composed of heterogeneous compounds, which greatly contribute to its function as a physical and immunological defense mechanism. The outer mucus layer is composed of trillions of commensal bacteria, antimicrobial proteins, defensins, and secretary immunoglobulin A; the central single cell layer houses specific epithelial cells being composed of enterocytes, goblet cells, and endocrine cells; and the inner layer is lamina propria that lodges the adaptive and innate immune cells, which includes, macrophages, dendritic cells, intraepithelial dendritic cells, plasma cells, cluster of differentiation 4+ (CD4+) T helper (Th) cells lymphocytes, T regulatory cells, and bone marrow cells (B cells) (De Santis et al., 2015; Vancamelbeke & Vermeire, 2017).

The mucus layer is generally considered to be the first line of physical defense against infection where the invaders are trapped when making direct contact with the epithelial cells (Rinninella et al., 2019). The mucus layer is made up of glycosylated mucin proteins, which form a gel-like consistency covering the gut epithelium (Vancamelbeke & Vermeire, 2017). The glycosylated mucin (mucin 2 [MUC2]) is the most abundant mucus protein synthesized by goblet cells present throughout the small and large intestine. An increased level of MUC2 secretion is the first line of physical defense against colitis and other gut-associated diseases (Van der Sluis et al., 2006). The colon has two mucus layers, with the thin outer layers generally permitting long-term colonization by commensal bacteria, whereas the thick inner layer is devoid of said commensal bacteria (Vancamelbeke & Vermeire, 2017). Antimicrobial proteins, defensins, and secretory immunoglobulin A are often released into the mucus layer to support the physical separation of the microbiota between the epithelium and the lumen. The composition of the mucus layer can affect the functional activities of gut microbiota, whereas the microbiota can also regulate the properties of the mucus layer (Johansson et al., 2015).

Epithelial cells are positioned beneath the mucus layer, also acting as another durable determinant of the physical intestinal barrier. These epithelial cells often regulate the transport of all lipophilic and larger molecules through the three junctional complexes, adherens junctions (AJs), tight junctions (TJs), and desmosomes (Vancamelbeke & Vermeire, 2017). TJ and AJ together form the apical junction complex (AJC), which provides selective barrier permeability and cell polarity (Figure 1).

TJ is the adhesive mixture that mostly covers the intercellular space, containing membrane proteins (zonula occludens [ZO]-1, 2, 3), transmembrane proteins (occludin, claudins, MARVEL domain-containing 3 protein, junctional adhesion molecule 1 [JAM-A], tricellulin, and lipopolysaccharide-stimulated lipoprotein receptor), and several regulatory proteins such as symplekin, 7H6, cingulin, etc. (Guzman et al., 2013). AJ is located underneath TJs and is mainly involved in the assembly. AJ regulates the integrity of the epithelium through strong ties with desmosomes. AJC is eventually connected to actin and myosin, which allows the maintenance of the junctions, barrier homeostasis, and intracellular signaling pathways (Turner, 2009; Vancamelbeke & Vermeire, 2017). In addition to orchestrated arrangements, the commensal gut bacteria also play a dynamic function in regulating host barrier homeostasis by maintaining cell renewal, stimulating wound healing repair, and restructuring the TJ (Guzman et al., 2013). TJ stability is essential for the regulation of barrier integrity, and the gut epithelial cells in the...
FIGURE 1  Organization of the intestinal epithelial barrier integrity

TJ formation are thus renewed at every 4–5 days’ intervals (Vereecke et al., 2011).

3  |  GUT MICROBIOTA AND THE INTESTINAL EPITHELIAL BARRIER

The gut is the vast reservoir of multifaceted microorganisms, collectively known as gut microbiota, which includes about $10^{12}$ bacteria in the distal portion of the gut (Martins dos Santos et al., 2010). These bacteria are diverse, comprising approximately 1150 species, with around 160 species shared between individuals, with Firmicutes (60%) and Bacteroidetes (10%) as the dominant two phyla (Alneberg et al., 2014; Qin et al., 2010). Actinobacteria, Proteobacteria, Cyanobacteria, Fusobacteria, and Verrucomicrobia are phyla with lower levels of abundance in the healthy gut. These bacterial communities often facilitate food digestion and regulate the immune system and a healthy gut environment (Ganesan et al., 2018). The composition of gut microbiota varies according to the diet and environment (Table 1).

Mucus seals the gut epithelium, acting as a diffusion barrier and preventing a high volume of antibacterial products from approaching the cell surface, ultimately protecting the intestinal tract (Johansson et al., 2013; Vaishnava et al., 2011). The mucus in the small intestine helps prevent microbial entry as well as assisting the development of immunity in the host (Johansson & Hansson, 2011; Shan et al., 2013). The thicker inner mucus layer can be detected in the gut region of the mouse and human, with this layer of the protection system separating the bacteria from the tissue (Shan et al., 2013).

Elements of the microbiota, such as Bacteroides, Blifidobacteria, and Akkermansia muciniphila, often exist in nonattached forms in the outer mucus of the gut, where they can break down and use mucin glycans as a primary energy source. The degradation of mucin glycans provides the intestinal tract with a stable resource that may provide up to 50% of the carbon flux (Ganesan et al., 2018). The secretion of exoglucosidases regularly takes place in specific genetic loci for definite kinds of substrates, namely, starch, cellulose, and xylose-containing polysaccharides (Johansson et al., 2010; Larsbrink et al., 2014). These mucin glycans normally shield the mucin polymer from redundant degradation. However, the inner mucus layer is more susceptible to gut-associated pathologies and may be rapidly degraded allowing bacteria to reach the epithelium and elicit inflammation (Fu et al., 2011; Johansson et al., 2015). The germ-free mucus is found in both the small and large intestines, and in recent times this colon mucus has been identified as being reliant on the composition of the microbiota. Evidence has shown that although microbiota and hosts have a limited connection, there are massive interactions and communications between them (Jakobsson et al., 2014; Johansson et al., 2015).

The composition of the gut microbiota varies greatly according to diet, lifestyle, age, gender, ethnicity, body mass index, and dietary behaviors. This variation is usually noticed in the form of physiological implications in the healthy gut setting, as well as in intestinal and extra-intestinal disorders. The gut microbiome usually acts as a metabolic organ, producing various bioactive metabolites, including trimethylamine-N-oxide (TMAO), short-chain fatty acid, and bile acids that can disturb the normal physiological functions of the host. Several animal and clinical studies have shown that numerous families of bacteria, namely, Deferribacteraceae, Anaeroplasmataceae, Prevotellaceae, and Enterobacteriaceae, are involved in the production of TMAO (Craciun & Balskus, 2012; Koeth et al., 2013; Zhu et al., 2014). Additionally, two different phyla such as Firmicutes and Proteobacteria that represent
### Table 1: The richness of intestinal microbial communities

| Enterotypes in healthy gut individuals | Actinobacteria | Proteobacteria | Bacteroidetes | Firmicutes | Verrucomicrobia | References |
|----------------------------------------|----------------|----------------|---------------|------------|----------------|------------|
| 1Slackia                               | 1Geobacter     | 1Bacteroides   | 1Ruminococaceae | 1Akkermansia muciniphila | Arumugam et al., 2011 |
| 1Eggerthella                           | 1Desulfovibrionaceae | 1Prevotella | 1Alkaliphilus | 1Bifidobacterium vulgatus | Bai et al., 2018; Iizumi et al., 2017; Lozupone et al., 2012; Pérez-Cobas et al., 2013 |
| 1Gordonibacter                         | 1Rhodospirillum | 1Parabacteroides | 1Catenibacterium | 1Ruminococcus | 1Bifidobacterium | Bai et al., 2018; Iizumi et al., 2017; Lozupone et al., 2012; Pérez-Cobas et al., 2013 |
| 1Helicobacter                          | 1Escherichia   | 1Sphingobacterium | 1Clostridiales | 1Staphylococcus | 1Enterobacteriaceae | Karlsson et al., 2012; Pérez-Cobas et al., 2013 |
| 1Shigella                              | 1Slackia       | 1Geobacter     | 1Prevotella   | 1Clostridiales | 1Succinivibrio | De Filippo et al., 2010; Pérez-Cobas et al., 2013 |
| 1Gordonibacter                         | 1Helicobacter  | 1Sphingobacterium | 1Clostridiales | 1Succinivibrio | 1Succinivibrio | Bervoets et al., 2013; Borgo et al., 2017 |
| 1Shigella                              | 1Slackia       | 1Geobacter     | 1Prevotella   | 1Succinivibrio | 1Succinivibrio | Bervoets et al., 2013; Borgo et al., 2017 |
| Obese individuals                      | ↑Bifidobacterium | ↓Proteobacteria | ↓Bacteroides | ↑Lactobacillus | ↑Akkermansiae | |
| Underweight individuals                | ↑Enterobacteriaceae | 1Bacteroides | 1Ruminococaceae | 1Akkermansiae | 1Bifidobacterium | De Filippo et al., 2010; Pérez-Cobas et al., 2013 |
| Individuals in high-performance sport  | ↑Succinivibrioae | 1Bacteroides | 1Ruminococaceae | 1Akkermansiae | 1Bifidobacterium | De Filippo et al., 2010; Pérez-Cobas et al., 2013 |
| High-fiber diet (African diet)          | ↓Bifidobacterium | ↑Prevotella | 1Eubacterium | 1Bifidobacterium | 1Roseburia | Bervoets et al., 2013; Borgo et al., 2017 |
| High-fat diet (Western diet)            | Actinobacteria | ✱Bilophila | Bacteroides | 1Roseburia | ↑Eubacterium rectale | Arumugam et al., 2011 |
|                                       | ✱Alistipes | ✱Barnesiella | ✱Geoobserver | ✱Eubacterium rectale | ✱Barnesiella | Arumugam et al., 2011 |
九种细菌物种，包括Proteus penneri, Edwardsiella tarda, Providencia rettgeri, Clostridium asparagiforme, Clostridium hathewayi, Clostridium sporogenes, Anaerococcus hydrogenalis, Desulfovibrio desulfuricans, and Escherichia fergusonii，也提供了显著的TMAO生产（Craciun & Balskus, 2012; Romano et al., 2015）。这种菌群失调被认为是由肠黏膜组织的变化引起的，也可能导致多种代谢和炎症性疾病。

4 | INTESTINAL EPITHELIAL BARRIER DYSFUNCTION

The importance of the gut epithelial barrier in disease pathogenesis has recently become a fascinating theme. Alterations in the integrity of the intestinal barrier can be detected in both intestinal and systemic diseases, such as metabolic disorders, inflammatory diseases, and systemic/extra-intestinal disorders (Chelakkot et al., 2018; Mu et al., 2019; Oshima & Miwa, 2016). Nevertheless, researchers have not reached a consensus over whether the loss in barrier integrity is the reason or result of these diseases. A low-fiber diet, exogenous pathogens, environmental stress, and certain medications may be critical factors leading to physiological abnormalities and the loss of barrier integrity (Figure 2). An imbalance in gut microbiota and intestinal dysfunction is greatly associated with several chronic diseases, such as irritable bowel syndrome, IBD, celiac disease, non-alcoholic fatty liver disease, diabetes, obesity, hypertension, cardiac failure, atherosclerosis, renal diseases, colorectal cancers, autism spectrum diseases, Alzheimer’s and Parkinson’s diseases, multiple sclerosis, and hepatic encephalopathy (Ganesan et al., 2018, 2019; Ganesan & Xu, 2018a, 2019; Rinninella et al., 2019; Zhang et al., 2018). These microbial populations, in tandem with the mucus layers, often inhibit invading pathogenic bacteria from establishing host infections (Liu et al., 2020; Shalapour & Karin, 2020).

5 | DIETARY PHYTOCHEMICALS

Dietary phytochemicals are constituents of natural foods and dietary supplements that serve both basic human nutritional needs and provide changes in health status (Ganesan & Xu, 2017c, 2018b). These compounds are abundant in plants, and many have been used as primordial traditional medicines, including polyphenols, terpenoids, alkaloids, and phenolics (Mickymaray & Alturaiki, 2018; Mickymaray et al., 2016; Nair et al., 2016; Pandian et al., 2006; Sukalingam et al., 2017). The dietary phytochemicals most often presented to be effective against numerous diseases include apigenin (parsley), baicalein (Indian trumpet), curcumin (turmeric), diallyl sulfide (onion), ellagic acid (pomegranate), epigallocatechin-3-gallate (EGCG) (green tea), genistein (soybean), gingerol (ginger), isothiocyanates (cruciferous vegetables), lycopene (tomatoes), quercetin (leafy vegetables, broccoli), resveratrol (grapes), rosmarinic acid (rosemary), silymarin (milk thistle), sulforaphane (cruciferous vegetables), and catechins (green tea). These phytochemicals promote weight management and reduce the risk of obesity, diabetes, cardiovascular disease, neurodegenerative diseases, cancer, and antimicrobial and inflammatory diseases (Celik & Sanlier,
5.1 Dietary phytochemicals modulate gut microbiota and intestinal epithelial barrier

The gut microbiota can be recognized as a critical regulator of the IP. Several animal studies have demonstrated that the gut microbiota directly affects intestinal permeability by affecting TJ properties that subsequently promote epithelial barrier dysfunction and modulate low-grade inflammation (Ganesan et al., 2018, 2019; Mu et al., 2019; Shi et al., 2019). It has been confirmed that microbial dysbiosis can often elevate the production of bacterial lipopolysaccharide (LPS) and enhance intestinal permeability with an increased risk of inflammation and systemic endotoxemia. In immune cells, these LPS have been proved to stimulate nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) production by activating the Toll-like receptor 4 inflammatory cascade (Chelakkot et al., 2018). Hence, the prevention of microbial dysbiosis and the management of the complex gut microbial ecosystem have been projected as a novel approach to renovating the intestinal epithelial barrier (Damiano et al., 2018).

Dietary phytochemicals are bioactive substances that are extensively present in vegetables, fruits, and spinach. They are rapidly absorbed in the gut and extensively metabolized by gut microbiota. Based on the poor bioavailability of the compounds, their detoxification process quickly occurs in the liver and kidneys via methylation, glucuronidation, and sulfation (Damiano et al., 2018). Hence, the blood availability of the native compounds is reasonably low, compared to their metabolites. These metabolites have been extensively investigated for their copious biological activities, including antidiabetic, antiobesity, antimicrobial, antioxidant, anticancer, and anti-inflammatory functions (Ganesan & Xu, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f; Cardona et al., 2013; Joseph et al., 2015; Luescher et al., 2017). Besides, dietary phytochemicals have been recognized as averting the activation of NF-κB and the triggering of NF-κB through inhibiting inhibitor of nuclear factor kappa B (IkB) kinase phosphorylation and inhibiting proteasomal degradation (Edwards et al., 2017; Luescher et al., 2017). On the contrary, dietary phytochemicals have been investigated for their susceptibility to prevent the occurrence of NF-κB through inhibiting activator of nuclear factor kappa B (IkB) kinase phosphorylation and inhibiting proteasomal degradation (Edwards et al., 2017; Luescher et al., 2017). Besides, dietary phytochemicals (berberine, chrysins, curcumin, daidzein, EGCG, genistein, hesperetin, kaempferol, luteolin, naringenin, myricetin, quercetin, and morin) have presented modulation of intestinal barrier function via the prevention of multiple protein kinases, namely, phosphoinositide 3-kinases (PI3K)/serine/threonine-specific protein kinase (Akt), tyrosine kinase, protein kinase C (PKC), myosin light-chain kinase (MLCK), MAPK, and AMP-activated protein kinase (Table 2; Figure 3). This modulation helps regulate significant barrier functions in epithelial tissues, principally via regulating TJ expression (Gilsanz et al., 2016; Johansson et al., 2015; Kaulmann & Bohn, 2016; Shimizu, 2017).

Most outcomes have been obtained in in vitro and animal models, where the dietary phytochemicals have assisted in up- or downregulating central genes contributing to inflammatory mechanisms. Concerning clinical investigations, recent literature recommends that dietary phytochemicals could modulate intestinal epithelial barriers through various direct or indirect impacts related to the gut environment and immune system (Lobo de Sá et al., 2019). These kinds of investigations are still in their early stages in the few clinical studies presented. In the meantime, comprehensive animal studies are required to enhance the understanding of the relationship between the food–gut microbiota
| Dietary phytochemicals | Dosages used | Models | Key findings | Results | References |
|------------------------|-------------|--------|--------------|---------|------------|
| **Astilbin**           | 12.5 and 50 μM | Caco-2 cell | Astilbin increases TER, expression of claudin-1, ZO-2, occludin, TNF-α, IFN-γ. | Enhances TJ-related molecules and gut barrier | Nakahara et al., 2017 |
| **Baicalein**          | 1, 5, 10, 20, and 40 μM/L | Female BALB/c mice | Baicalein attenuates serum IgE, effector T cells, and cytokines and induces the differentiation of Treg cells via aryl hydrocarbon receptors. | Induces Treg differentiation and enhances barrier function | Bae et al., 2016 |
| **Cecropin A**         | 3.125, 6.25, and 12.5 μg/ml | IPEC-J2 | Cecropin A enhances TER, ZO-1, claudin-1, and occludin expression and downregulates the expression of TNF-α, IL-6, IL-8, and MAPK/ERK pathways. | Enhances intestinal epithelial cell barrier function | Zhai et al., 2018 |
| **Chlorogenic acid**   | 5, 25, 50, 100, 200, and 400 μM | MC3T3-E1 | Chlorogenic acid enhances cell viability and increases activities of GSH, NO, and decreased levels of intracellular ROS, MDA, and apoptosis. Also, it upregulates PI3K-Akt, caspase-3, and Nrf2 phosphorylation and expression levels of HO-1. | Prevents intestinal epithelial barrier dysfunction | Han et al., 2017 |
| **Chrys in, daidzein, genistein, hesperetin, luteolin, morin, and naringenin** | 100 μmol/L | Caco-2 | Flavonoids enhance TER and the expression of cytoskeletal associated TJ proteins, ZO-1, ZO-2, occludin, junctional adhesion molecule-1, and claudins. | Regulates intestinal TJ barrier integrity | Noda et al., 2012 |
| **Curcumin**           | 5, 20, and 80 μM | Caco-2 | Curcumin attenuates H2O2-induced disruption of paracellular permeability and enhances intestinal epithelial barrier function. Also, it upregulates claudin-1. | Protects human intestinal epithelial cells against H2O2-induced disruption of TJ and barrier dysfunction | Vashisht et al., 2017; Wang et al., 2012 |
| **Curcumin**           | 10 μM | IPEC-J2 cells & piglets | Curcumin elevates mitophagy and cell viability and enhances the activities of SOD CAT, and decreased levels of intracellular MDA and apoptosis. Also, it upregulates the AMPK–TFEB signal pathway. | Enhances intestinal barrier function and mitochondrial function | Cao et al., 2020 |
| **Quercetin**          | 50, 100, 150, and 200 μmol/L | Caco-2 | Quercetin increases TER and expression of TJ protein, ZO-1, and occludin. | Attenuates paracellular hyperpermeability and protects intestinal epithelial barrier | Majima et al., 2015 |
| **EGCG, genistein, myricetin, and quercetin** | 100 μmol/L | Caco-2 | Flavonoids protect the TJ barrier function against oxidative stress, acetaldehyde, enteric bacteria, and inflammatory cytokines. | Protects intestinal TJ barrier function | Suzuki & Hara, 2009 |
|**Eleutheroside B**     | 0.05, 0.10, and 0.20 mg/ml | IPEC-J2 cells | Eleutheroside B increases TJ protein, IL-10, and TGF-β and decreases cellular membrane permeability and expression of IL-6, IFN-γ, and TNF-α. | Increases intestinal barrier function, TJ protein expression | Che et al., 2019 |

(Continues)
| Dietary phytochemicals | Dosages used | Models | Key findings                                                                                                                                                                                                 | Results                                                                                       | References               |
|------------------------|-------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------|
| Ferulic acid           | 5, 10, and 20 μM | IEC-6 cells | Ferulic acid elevates cell viability and enhances the activities of GSH, SOD, and NO and decreased levels of intracellular ROS, MDA, and apoptosis. Also, it upregulates PI3K–Akt and Nrf2 phosphorylation and expression levels of HO-1. | Protects from heat stress-induced intestinal epithelial barrier dysfunction                      | He, Guo, et al., 2018    |
| Fucoidan               | 0, 0.1, 1.0, or 2.5 mg/ml | Caco-2 | Fucoidan enhances intestinal epithelial barrier function by upregulating the expression of claudin-1 and 2.                                                                                                    | Protects oxidative stress-induced barrier disruption                                        | Iraha, 2013              |
| Hirsutenone            | 10 μM       | Caco-2 | Hirsutenone reduces the expression of ZO-1 and increases Akt, HO-1, and tyrosine phosphorylation of the EGFR through EGFR/Akt- and ERK1/2-dependent pathways.                                                    | Improves barrier function                                                                    | Seo et al., 2014         |
| Kaempferol             | 100 μmol/L  | Caco-2 | Quercetin increases intestinal barrier integrity through the assembly of actin cytoskeletal-associated proteins, ZO-1 and 2, occludin, and claudin-1, 3, and 4.                                     | Protects intestinal TJ integrity                                                             | Suzuki & Hara, 2011      |
| Lentinan               | 100–500 mM  | Piglet | Lentinan improves intestinal morphology and barrier function, inhibits expression of inflammatory signaling pathways (TLR4) and pro-inflammatory cytokines (TNFα, IL-1β, and IL-6), and upregulates HSP 70. | Promotes intestinal health                                                                   | Wang et al., 2019        |
| Lignosulfonic acid     | 100 and 500 ng/ml | Caco-2 | Lignosulfonic acid enhances TER, claudin-2, IL-1β, and IL-6 and reduces the expression of IFN-γ, NF-κB, and TNF-α.                                                                                          | Beneficial for the treatment of inflammation-induced intestinal barrier dysfunction          | Matsuhisa et al., 2017   |
| Naringenin             | 10–100 μM   | Caco-2 | Naringenin enhances barrier integrity through Sp1-dependent transcriptional regulation and expression of claudin-4.                                                                                          | Regulates intestinal TJ functions                                                            | Noda et al., 2013        |
| Oregonin               | 50, 80, and 100 μM | HT-29 cells | Oregonin reduces the expression of COX-2, ICAM-1, IL-8, IL-1β, and NF-κB and increases HO-1 through the ERK1/2- and JNK-dependent signaling pathways.                                                          | The potential candidate for the treatment of IBD by preventing mucosal inflammation and barrier disruption. | Chi, et al., 2018        |
| Punicalagin            | 2.5, 5, 10, 20, or 40 μM | IEC-6 cells | Punicalagin elevates cell viability and enhances the activities of GSH, SOD, and NO and decreased levels of intracellular ROS, MDA, and apoptosis. Also, it upregulates PI3K–Akt and Nrf2 phosphorylation and expression levels of HO-1. | Protects intestinal epithelial barrier from oxidative stress                               | Xu et al., 2016          |
| Quercetin              | 50, 100, 150, and 200 μmol/L | Caco-2 | Quercetin increases TER and expression of TJ protein and claudin-4.                                                                                                                                               | Maintains intestinal TJ functions                                                             | Amasheh et al., 2008     |

(Continues)
| Dietary phytochemicals | Dosages used | Models | Key findings | Results | References |
|------------------------|-------------|--------|--------------|---------|------------|
| Quercetin              | 100 μmol/L  | Caco-2 | Quercetin enhances intestinal barrier function through inhibition of protein kinase C delta and assembly of claudin-1 and 4, ZO-2, and occludin. | Conserves intestinal TJ functions | Suzuki & Hara, 2009 |
| Quercetin and 2,3-dihydroxybenzoic acid | 50, 100, 150, and 200 μmol/L | Caco-2 | Quercetin increases TER and expression of ZO-1 and occludin. | Maintains TJ functions | Amasheh et al., 2009 |
| Resveratrol            | 1, 10, and 20 μM | Caco-2 and male Wistar rats | Resveratrol enhances intestinal epithelial barrier function by initiating the expression of HO-1-dependent signaling. It inhibits H2O2-induced protein kinase C activity and p38 phosphorylation. | Protects intestinal epithelial barrier | Wang et al., 2016 |
| Resveratrol            | 5, 20, and 80 μM | IPEC-J2 | Resveratrol enhances cell viability and increases expression of TJ proteins (claudin-1, occludin, and ZO-1), improves activities of SOD-1, CAT, and GSH-Px, and decreased levels of intracellular ROS, and apoptosis. Besides, it upregulates PI3K–Akt and Nrf2 phosphorylation and expression levels of antioxidant genes HO-1, SOD-1, and CAT. | Protects intestinal epithelial integrity | Zhuang, Wu, et al., 2019 |
| Rhein                  | 4 μM        | IEC-6 cells | Rhein enhances cell viability and increases activities of SOD, CAT, GSH, and GST, and decreased levels of intracellular ROS, and apoptosis. Also, it upregulates PI3K–Akt, Nrf2 phosphorylation, and expression levels of HO-1. | Protects intestinal epithelial barrier | Zhuang, Yu, et al., 2019 |
| Sulforaphane           | 2.5, 5, 10 mg/kg | Male C57BL/6 mice, Caco-2 cells | Sulforaphane normalizes gut microbiota dysbiosis, enhances the upregulation of TJ proteins, and GLP2 decreases IL-6 and secretory IgA. | Normalizes gut flora and enhances gut barrier | He, Huang, et al., 2018 |
| Thymol                 | 10-100 mM   | IPEC-J2 cells | Thymol blocks ROS production, enhances TER, ZO-1, and reduces IL-8 and TNF-α. | Improves barrier function and attenuates inflammatory responses | Omonijoo, et al., 2018 |

Abbreviations: Akt, serine/threonine-specific protein kinase; AMPK, adenosine 5′-monophosphate-activated protein kinase; CAT, catalase; COX-2, cyclooxygenase-2; EGCG, epigallocatechin gallate; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; GLP2, glucagon-like peptide-2; GSH, glutathione; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinases; ROS, reactive oxygen species; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; Treg, regulatory T cells; ZO, zonula occludens.

and intestinal epithelial barrier, feasibly via control-based dietary intervention studies. Additionally, effort is required to describe the consistency of the existing biomarkers of the intestinal epithelial barrier and the possible manipulation of novel and/or improved biomarkers.

### 6 | AUTOIMMUNE DISEASES

The immune system plays a necessary function in the demolition of unsolicited non-self-cells and defends the host against invading microorganisms. Any disruption in this progression, and uncontrolled
Dietary phytochemicals modulate intestinal epithelial barrier at various physiological levels: (1) Luminal level: Absorption and activation of dietary phytochemicals; modulation of intestinal microorganism composition and endotoxin; and production of short-chain fatty acids. (2) Intracellular level: Maintenance and expression of various intestinal proteins, namely, tight junction, adherents junction, gap junction, and desmosomes; upregulation of multiple protein kinases (protein kinase C [PKC], phosphoinositide 3-kinases [PI3K]/serine/threonine-specific protein kinase [Akt], tyrosine kinase, nuclear factor erythroid 2-related factor 2 [Nrf-2], myosin light-chain kinase [MLCK], mitogen-activated protein kinase [MAPK]); and downregulation of nuclear factor-kappa B (NF-kB) and Toll-like receptor 4 (TLR4). (3) Systemic level: Reduction of pro-inflammatory mechanisms and regulation of the host immune system.

immune reactions that attack the host body’s tissues, may eventually lead to autoimmunity. Thus, autoimmunity is known as the disturbance of antigenic recognition and challenging to remove by the host immune cells (Rengasamy et al., 2019). Failure of these recognition and removal mechanisms leads to a disparity in the activation and maintenance of immune cells, especially lymphocytes, which is thought to be the main step in the development of ADs (Khan et al., 2019). Various contributors interplay in the pathogenesis of AD, including hereditary and environmental factors (Venkatesha et al., 2016). The pathology of uncontrolled autoimmune reactions may cause severe disabilities or malformations, and eventually total loss of organ functions.

The prevalence of the diseases is increased in developed nations, compared to in developing nations (Hughes et al., 2016). AD can be classified into two categories: (1) organ-specific: the autoimmune process is fixed against a single organ, for example, type 1 diabetes mellitus (T1DM), IBD, and psoriasis (Mastrandrea, 2015), and (2) systemic autoimmune disorders: where the immune response attacks multiple organs at the same time, for example, rheumatoid arthritis (RA), amyotrophic lateral sclerosis (ALS), and systemic lupus erythematosus (SLE) (Schwartz & Shechter, 2010; Wahren-Herlenius & Dörner, 2013). Due to their long-term complications, ADs impose a greater social burden in social, economic, and psychological terms. The conventionally used allopathic medicines for managing AD are greatly associated with severe adverse reactions. These commercial drugs are very expensive and unaffordable for many patients (Venkatesha et al., 2016). Thus, there is consistent demand for relatively cost-effective alternatives to conventional drugs for AD. Against this background, natural dietary phytochemicals represent a dynamic and auspicious source for categorizing novel therapeutic agents for AD.

Plant products are generally the primary sources of dietary phytochemicals with beneficial effects, of which numerous compounds have ultimately been established in medicine consumed globally for varied illnesses, including inflammatory, autoimmune, and infectious diseases, metabolic and neurodegenerative diseases, and cancer (Banu & Kumar, 2009; Islam et al., 2019; Jayachandran et al., 2019; Kumar, Banu, et al., 2006; Kumar, Sharmila Banu, et al., 2008; Kumar, Sharmila Banu, Ganesan Murugesan, et al., 2007; Pandian et al., 2006; Pandian et al., 2006; Sinaga et al., 2016; Sukalingam et al., 2018). Additionally, numerous dietary phytochemicals belonging to the various traditional medicine systems (Chinese, Japanese, Indian, Turkish, Egyptian, African, and others) have been used by various peoples with AD, with or without the knowledge of primary general practitioners, for their beneficial potential (Hughes et al., 2016; Mahmoodi et al., 2019; et al., 2016; Rengasamy et al., 2019; Xiao et al., 2018).

Dietary phytochemicals have been widely used in the prevention and treatment of various ADs including T1DM, IBD, psoriasis, RA, ALS, and SLE (Mahmoodi et al., 2019; Mastrandrea, 2015; Rengasamy et al., 2019; Xiao et al., 2018; Zhang et al., 2015). A list of the various dietary phytochemicals, the dosages used, target cells, and their mechanism against ADs has been provided in Table 3. Dietary phytochemicals...
| Dietary phytochemicals | Dosages used | Effector cells | Activity | Autoimmune Diseases | References |
|------------------------|--------------|----------------|----------|---------------------|------------|
| Morroniside            | 100 μM       | Human neuroblastoma cells | Elevation of cellular GSH accompanied by marked protection against H₂O₂-mediated toxicity, reduced the release of LDH, maintained the stability of the cell and mitochondrial membrane potential, inhibited the SOD activity and the formation of ROS, and upregulated the expression of Bcl-2 | ALS | Wang et al., 2007, 2009 |
| EGCG                   | 1.5, 2.9, and 5.8 mg/kg/day, 60 days, p.o. | Motor neurons | Delayed the onset of symptoms of neurodegeneration and prolonged the life span; downregulation of Bax expression and upregulation of Bcl-2 | ALS | (Koh et al., 2006) |
| Madecassoside          | 61.1 and 185.6 mg/kg/day, 90 days, p.o. | Motor neurons | Protect motor neurons from degenerating and could also increase the longevity of these mice. | ALS | Kumar et al., 2019 |
| Allicin                | 80 mg/kg/day | Motor neurons | Prolonged life span and delayed the onset of symptoms of neurodegeneration, activated HO-1, a phase II detoxifying enzyme that has been revealed to play an active role in a protective endogenous mechanism, especially against oxidative and inflammatory insults. | ALS | (Calo et al., 2010; Guo et al., 2011) |
| Ampelopsin             | 100 μM       | Pheochromocytoma | Protect neuron cells against H₂O₂-elicited oxidative damage through attenuation of ROS production, induction of HO-1 protein expression, inhibition of caspase-3, and upregulation of HO-1 expression with the activation of ERK1/2- and Akt-dependent signaling pathways. | ALS | (Kou et al., 2011) |
| Resveratrol            | 25 mg/kg/ day, for 4 weeks, p.o. | UC | Reduction of mucosal inflammation by decreasing malondialdehyde, COX-2, PGE-synthase 1, TGF-β, and neutrophil infiltration and increasing glutathione peroxidase activity, *Bifidobacteria*, and *Lactobacillus*. | IBD | (Alrafas et al., 2019; Galvez et al., 2014; Kaur et al., 2016; Larrosa et al., 2010; Martins dos Santos et al., 2010; Yildiz et al., 2015) |
| Gallotannins and gallic acid | 200–400 g for 8 weeks | The pilot study in UC patients | Decreased the plasma levels of pro-inflammatory cytokines, IL-8, growth-regulated oncogene, and granulocyte-macrophage colony-stimulating factor, significantly increasing the abundance of *Lactobacillus* spp., *Lactobacillus plantarum*, *Lactobacillus reuteri*, and *Lactobacillus lactis*. | IBD | Kim et al., 2020 |

(Continues)
| Dietary phytochemicals | Dosages used | Effector cells | Activity | Autoimmune Diseases | References |
|------------------------|--------------|----------------|----------|----------------------|------------|
| Chlorogenic acid       | 1000 mg/kg for 3 months | UC             | Decreased serum D-lactate and diamine oxidase and enhanced the expression of the claudin-1 protein in the small intestinal epithelium, decreased the mucosa histamine, tryptase, and tryptase-positive mast cell counts, downregulated IL-1β, IL-6, TNF-α, and NF-κB in jejunal and ileal mucosa, decreased MDA, increased GSH-Px and CAT, and elevated Nrf2 and HO-1 in duodenal and jejunal mucosa. | IBD | Chen et al., 2018 |
| Epigallocatechin gallate | 0, 3.6, 12.5, 25, and 50 mM | Salivary acinar cells | A decrease in TNF-α-induced damage of salivary acinar cells. | Murine Sjogren’s syndrome | (Hsu et al., 2007) |
| Resveratrol            | 10-50 mg/kg/day, for 4 weeks, p.o. | Skin damage | In vitro induction of keratinocyte apoptosis via Sirt-1 activation and keratinocyte inhibition via decrease of aquaporin 3 activations. In an in vivo model of murine psoriasis, it decreases mRNA expression of IL-17 and IL-19, thus, mitigating skin damage. | Psoriasis | Lee et al., 2015 |
| Resveratrol            | 100 μM | Rat RSC-364 synovial cells | Blockade of p38 and JNK pathways and decrease of ROS and inflammatory markers | RA | Gehr et al., 2013 |
| EGCG                   | 10 mg/kg/ three times per week p.o. | Mouse Joints and hind and the forepaws | Ameliorated swelling, redness, and erythema of the hind paws and the forepaws, decreased IL-6, TNF-α, IFN-γ, CD4 T, and CDB T cells as well as B cell, and increased IL-10, CD4+ CD25+ FoxP3+ Treg in draining lymph nodes; increased Nrf-2 and HO-1 in joints. | RA | Min et al., 2015 |
| Naringenin             | 100 or 200 mg/kg/day p.o. | Mouse Joints, cartilages and ankle tissues, splenocytes | Reduced arthritis severity, bone erosion in ankle joints, cartilage destruction, infiltrating inflammatory cells, synovial hyperplasia, decreased collagen-specific antibodies, reduced frequency of CD4+ IFN-γ+ Th1 and CD4+ IL-17A+ Th17 cells in splenocytes, reduced RNA expression of Th11 and Th17-related transcription factor in the spleen. | RA | Li et al., 2015 |
| Quercetin              | 30 mg/kg/day, p.o. | Mouse Joints and paw | Decreased TNF-α, IL-1β, IL-17, and MCP-1, ameliorated paw edema, reduced synovitis with moderate pannus formation and inflammatory cell infiltration in the knee, dwindled destruction of cartilage and bone. | RA | Haleagrahara et al., 2017 |

(Continues)
| Dietary phytochemicals | Dosages used | Effector cells | Activity | Autoimmune Diseases | References |
|------------------------|--------------|----------------|----------|---------------------|------------|
| Quercetin              | 150 mg/kg/day, p.o. | Rat Joints and ankle tissues | Reduced paw edema, arthritis index, and the histopathological score of ankle tissues, decreased IL-17A and IL-21 and induced IL-10 and TGF-β, reduced mRNA levels of IL-17A, IL-21, IL-23, and RORγt in bone tissues, increased IL-10, TGF-β, FoxP3, and Treg cells in draining lymph nodes; decreased proportion of CD4+ IL-17A+ T cells, reduced protein levels of NLRP3, caspase-1, and IL-1β, and increased HO-1 in the synovium, decreased serum levels of the inflammatory mediators TNF-α, IL-1β, IL-6, and PGE2 | RA | (Yang et al., 2018) |
| Silibinin              | 50-150 mg/kg/day, p.o. | Rat joints | Reduced joint inflammation, pannus formation, inflammatory cell infiltration, and bone erosion, decreased serum levels of TNF-α, IL-6, and IL-1β | RA | (Tong et al., 2018) |
| Kaempferol             | 2 mg/kg, i.p., three times per week | Mouse joints and cartilages | Decreased arthritis incidence and severity of inflammation, cartilage damage, and bone erosion; reduced osteoclastogenic activity in the joints and inhibited ex vivo osteoclast formation, decreased expression of IL-17, Aryl hydrocarbon receptor (Ahr), CCL20, and RORγt in draining lymph node cells, decreased number of CD4+/IL-17+, /pSTAT3+, and /Src+ splenic T-cells | RA | Lee, Moon, et al., 2018 |
| Curcumin               | 80 μM | Synovial joints | Decreased proteinuria, IgG1, IgG2a, and anti-dsDNA, suppressed TNF-α and MCP-1 in kidney and FoxP3 in the spleen | RA | Lee et al., 2012 |
| Resveratrol            | 25-50 mg/kg/day, for 4 weeks, p.o | Bone cartilage | In vitro, using fibroblast-like synoviocytes, decrease in NADPH oxidase activity, MMP release, RANKL and ROS generation with the increase in Sirt-1 mRNA; in experimental models, reduction of IL-17 and reduction of cartilage destruction. | RA | (Elmali et al., 2005; Hao et al., 2017; Rahal et al., 2012; Tian et al., 2013; Tsai et al., 2017) |
| Apigenin               | 20 mg/kg/day, 30days p.o. | Lupus nephritis | Suppressed IFN-γ and having anti-dsDNA, anti-ssDNA activity decreased IL-6, IL-17 in T and B cells, reduced Cox-2 | SLE | Kang et al., 2009 |
| Daidzein               | 2-20 mg/kg/day, 8 weeks, p.o. | Mice splenomegaly | Decreased anti-dsDNA and IFN-γ in mitogen-activated T cells from spleen | SLE | Hong et al., 2008 |
| Coumestrol             | 25-50 mg/kg 8 weeks, p.o. | Mice nephritis | Delayed onset of proteinuria and improved renal function by inhibited the TNF-α and IL-1β | SLE | Hong, Huang, et al., 2009 |
| Coumestrol             | 10-200 mg/kg 8 weeks, p.o. | Mice splenomegaly | Reduced the serum level of TNF-α, IL-6, and IL-1β in BALB/c mice | SLE | Hong, Chao, et al., 2009 |

(Continues)
| Dietary phytochemicals | Dosages used | Effector cells | Activity | Autoimmune Diseases | References |
|------------------------|--------------|----------------|----------|---------------------|------------|
| Coumestrol             | 10–200 mg/kg 8 weeks, p.o. | Mice splenomegaly | Suppressed I-6 and TNF-α production in macrophage and subsequently reduced splenomegaly and proteinuria | SLE | (Schoenroth et al., 2004) |
| Curcumin               | 0.1 and 1 μg/ml | CD4⁺ T cell cultures | Modulated the balance between Th17/Treg in CD4⁺ and reduced the Th17 response and IL-17A release, activated the TGF-β | SLE | (Handono et al., 2015) |
| Resveratrol            | 75 mg/kg/day for 2 months, p.o. | Glomerulonephritis | Decreased proteinuria, IgM, and IgG deposition in kidney, glomerulonephritis, and serum IgG1 and 2 | SLE | (Wang et al., 2014) |
| Indole-3-carbinol      | 72 mg/kg/day, p.o. | Glomerulonephritis | Increased life span by decreasing the proteinuria, glomerulonephritis, renal abnormalities, intestinal nephritis, and activation of B cell and T cells | SLE | (Yan et al., 2009) |
| Curcumin               | 5 mg/ml ultra-soluble turmeric for 10 weeks, p.o. | Mice lymphadenopathy | Inhibited proteinuria, salivary gland infiltration, lymphadenopathy | SLE and Sjögren’s syndrome | (Kurien et al., 2015) |
| Quercetin              | 15 mg kg/i.p. a day for 4 weeks | Rat pancreatic β-cells | Inhibit the production of erythrocyte MDA, serum NO, and pancreatic tissue MDA | T1DM | (Coskun et al., 2005) |
| Epicatechin            | 30 mg/kg/ twice a day for 6 days, p.o. | Rat pancreatic β-cells | Inhibit insulin release from islets | T1DM | (Kim et al., 2003) |
| Silymarin              | 100 μM | Rat pancreatic β-cells | Inhibited the production of inflammatory cytokine, IL-1β, IFN-γ, and TNF-α in macrophages and T-cells and protect from tissue destruction, reduce ROS production in host cells | T1DM | (Matsuda et al., 2005) |
| EGCG                   | 60–90 mg/kg day for 8 weeks, p.o. | Mouse pancreatic β-cells | Increase the insulin levels, anti-inflammatory cytokine IL-10, and inhibiting caspase-3 | T1DM | (Fu et al., 2010) |
| Anthocyanin            | 50 mg/kg, a day for 30 days, p.o. | Mouse pancreatic β-cells | Increase insulin resistance, level of serum insulin, and improved glucose utilization in tissue, stimulate the activation of tyrosine kinase activity and protect β-cells against apoptosis through upregulating Bcl-2 and downregulating Bax and caspase-3 | T1DM | (Nizamutdinova et al., 2009) |
| Genistein              | 0.4–20 μM | Mouse pancreatic β-cells | Enhance the glucose-stimulated insulin secretion and mass of β-cells in clonal insulin-secreting cell lines (INS-6 and MIN6), improve wound angiogenesis by suppressing SOD and FoxO1/iNOS pathway | T1DM | (Fu & Liu, 2009; Fu et al., 2012) |
| Hesperidin             | 100–200 mg/kg, a day for 12 weeks, p.o. | Diabetic retinopathy | Stimulate anti-inflammatory cytokine, inhibit blood glucose level through glucose regulating enzymes | T1DM | (Shi et al., 2012) |
| Chrysin                | 1–100 mg/kg/day, p.o. | autoimmune encephalomyelitis | Inhibit the p38 MAPK pathway and stimulate PPAR-α | T1DM | (Zhang et al., 2015) |

(Continues)
### Table 3 (Continued)

| Dietary phytochemicals | Dosages used | Effector cells | Activity | Autoimmune Diseases | References |
|------------------------|--------------|----------------|----------|----------------------|------------|
| Rutin and naringin     | 10 mg/kg/day, 28 days p.o. | Mouse pancreatic β-cells and testicular cells | Decrease MDA level and increase the level of antioxidants SOD and CAT | T1DM | (Akondi et al., 2011) |
| Resveratrol            | 250 mg/kg/day, p.o. | Mouse insulitis | Decrease of in vitro apoptosis via increased Sirt-1 expression. In vivo, in an obese model attenuation of insulitis due to diminished traffic of Th1 cells and macrophages from the periphery to pancreas and prevention of islet destruction | T1DM | Oliveira et al., 2017; You & Chatenoud, 2016 |

Abbreviations: ALS, amyotrophic lateral sclerosis; B cells, bone marrow cells; BcI2, B-cell lymphoma 2; CAT, catalase; CCL20, chemokine (C–C motif) ligand 20; CD4+, cluster of differentiation 4+; COX-2, cyclooxygenase-2; dsDNA, double-stranded deoxyribonucleic acids; ERK1/2, extracellular signal-regulated kinase 1/2; FoxO1, forkhead box O1; FoxP3, forkhead box P3; GSH, glutathione; H2O2, hydrogen peroxide; HO-1, heme oxygenase 1; IBD, inflammatory bowel diseases; IFN-γ, interferon gamma; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; mRNA, messenger ribonucleic acid; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; NO, nitric oxide; PGE2, prostaglandin E2; PPAR-α, peroxisome proliferator-activated receptor alpha; pSTAT3, phospho-Signal transducer and activator of transcription 3; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-κB ligand; RORγt, retinoic acid-related orphan receptor gamma; ROS, reactive oxygen species; Sirt1, Sirtuin-1; SLE, systemic lupus erythematosus; SOD, superoxide dismutase; Src+/-, signet ring cell features; T cells, thymus cells; TGF-β, transforming growth factor beta; Th17, T helper 17 cells; T1DM, type I diabetes mellitus; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; UC, ulcerative colitis.

### Figure 4

Dietary phytochemicals targeting various signaling pathways and attenuating autoimmune diseases are illustrated in Figure 4.

#### 7.1 Dietary phytochemicals attenuate the complications of T1DM

T1DM arises due to the obliteration of β-cells in the pancreatic islets of Langerhans, by macrophages, natural killer thymus cells (T cells), dendritic cells, and autoantigen-specific CD4+ and CD8+ T lymphocytes (You & Chatenoud, 2016), often generating inflammation in the tissue (Vives-Pi et al., 2015). This β-cells’ obliteration eventually leads to a deficiency in insulin and hyperglycemia (Skyler et al., 2016). Consequently, the development and outcomes of T1DM lead to ketoacidosis, renal failure, cardiovascular diseases, neuropathy, and retinopathy (Kumar, Banu, et al., 2008; Kumar & Murugesan, 2008; Kumar, Murugesan, et al., 2006; Kumar et al., 2009; Kumar, Sharmila Banu, Murugesan, et al., 2007). The mechanism involved in the immunological aspect of
the disease arises due to the inflammatory response. Hence, the production of TNF-α, IFN-γ, and nitric oxide (NO) by leucocytes inhibits the apoptosis of β-cells and the subsequent recruitment of APCs (Vives-Pi et al., 2015; Wällberg & Cooke, 2013; Zhang et al., 2020). APCs stimulate CD4+ T cells that trigger macrophages to discharge various cytokines and reactive oxygen species (ROS). These cascade mechanisms eventually bring about a pro-inflammatory environment that increases the cytotoxic effects on the islet cells (Vives-Pi et al., 2015; Wällberg & Cooke, 2013).

Dietary phytochemicals such as quercetin, epicatechin, silymarin, EGCG, anthocyanin, genistein, hesperidin, chrysins, rutin, naringin, and resveratrol inhibit the production of inflammatory cytokines, IL-1β, IFN-γ, and TNF-α in macrophages and T-cells and reduce ROS production in host cells eventually protecting from the destruction of pancreatic tissue (Akondi et al., 2011; Coskun et al., 2005; Fu & Liu, 2009; Fu et al., 2010, 2011, 2012; Nizamutdinova et al., 2009; Shi et al., 2012). Also, these compounds suppress NF-xB via the inhibition of various protein kinases—PI3K/Akt, MAPK, and protein tyrosine kinases (Fu & Liu, 2009; Fu et al., 2011, 2012; Lee et al., 2011). Therefore, the administration of dietary phytochemicals is auspicious as drugs for T1DM.

### 7.2 Dietary phytochemicals attenuate IBD

IBD is a set of immune disorders categorized by chronic inflammation in the intestine, with general forms of Crohn’s disease and ulcerative colitis (UC) (Chen et al., 2019). The disease can be distinguished by the locality, occurrence, deepness of the inflammation, and disease complications. Clinically, both CD and UC have the same symptoms, comprising diarrhea, hematochezia, and abdominal pain (Kim & Cheon, 2017). The etiology of IBD is not well-defined; however, it is recognized as having multifactorial pathogenesis. Various factors are thought to build toward the clinical signs of the diseases, including environmental, genetic, bacterial infection, disruption of the immune system, and chronic intestinal inflammation (Fakhoury et al., 2014). The evidence further recognized that oxidative stress also plays a pathogenic function in chronic inflammatory diseases (Chen et al., 2018; Guan & Lan, 2018). Macrophages and neutrophils generate higher amounts of ROS and reactive nitrogen species that can change the protein function, augment inflammation and cell death, and increase alteration in the gut mucosa environment (Tian et al., 2017).

The intestinal epithelial barrier plays a vital role in regulating human intestinal homeostasis. When it is altered, the products of the commensal gut microbiota translocate from the intestinal lumen to the wall, resulting in the stimulation of immune cells (Neurath, 2014). In IBD, deregulation of effector T cells arises in CD (Th1 and Th17) and in UC (Th2 and Th217), along with increased IL-17 providing an augmented inflammatory process in the lamina propria (Boirivant & Cossu, 2011). In CD, Th1 lymphocyte stimulation contributes to a release of IL-12, TNF-α, IFN-γ, and IL-23, whereas in UC, Th2 triggers the generation of IL-4, IL-5, IL-6, and IL-10 (Singh et al., 2012). Both in CD and UC, TNF-α is often found at higher levels that stimulate cell proliferation, differentiation, and apoptosis in intestinal endothelial cells via the recruitment and autolytic stimulation of caspases (Fakhoury et al., 2014).

Evidence has shown that dietary phytochemicals such as resveratrol, chlorogenic acid, gallo-tannins, and gallic acid are capable of inhibiting pro-inflammatory cytokines, IL-1β, IL-6, IL-12, TNF-α, and NF-xB; increasing GSH-Px and catalase (CAT); and elevating Nrf2 and HO-1 that neutralize ROS (Alrafas et al., 2019; Jayachandran et al., 2019; Kaur et al., 2016; Kim et al., 2020; Yildiz et al., 2015; Tong et al., 2018). Besides, these compounds modulate the gut microbiota and maintain the mechanisms of intestinal homeostasis (Galvez et al., 2014; Larrosa et al., 2010). Hence, the supplementation of dietary phytochemicals is promising as drugs for IBD.

### 7.3 Dietary phytochemicals attenuate psoriasis

Psoriasis is an immune-mediated, chronic, inflammatory disease that is stimulated by various factors including microbial infections and manifests in the skin, joints, tendons, ligaments, nails, and mucosal membranes (Di Nardo et al., 2018). It is mainly characterized by the appearance of red patches in the squamous layers. These cutaneous lesions are characterized by the hyperproliferation of epidermal cells and keratinocytes of the elbows, knees, scalp, and lumbar-sacral region that form along with inflammatory infiltrate (Dimitris et al., 2020). Psoriasis is generally activated by DNA fragments of keratinocytes conjugated with cathelicidin peptide LL-37, leading to immune complex development by recruitment of dendritic cells and T lymphocytes (Campbell et al., 2018). During the chronic phase, these triggered native dendritic cells generate cytokines (IL-12 and IL-23) related to psoriasis (Zorko et al., 2018). Furthermore, these cytokines support the production of Th1 and Th17, which elevate the expression of IL-12, IL-17, and IFN, the main cytokines in the progression of inflammatory diseases (Campbell et al., 2018; Dimitris et al., 2020). These elevated cytokines often cause the stimulation of keratinocytes that eventually promote cell proliferation and differentiation (Lowes et al., 2014). Although several topical and systemic clinical treatment choices exist for psoriasis (Di Nardo et al., 2018; Farahnik et al., 2016; Fioranelli et al., 2017), none provide excellent clinical outcomes without side effects.

Dietary phytochemicals are compounds that exhibit potential anti-inflammatory effects by reducing the generation of pro-inflammatory cytokines and promoting keratinocyte apoptosis. Administration of curcumin, EGCG, and resveratrol showed a reduction in pro-inflammatory markers such as TNF-α, IFN-γ, IL-2, IL-12, IL-17A, IL-17F, IL-22, and IL-23 in the plasma and tissues (Kang et al., 2016; Lee et al., 2015; Zhang et al., 2016). Treatment with these dietary phytochemicals attenuates skin inflammation, reduces infiltration of T cells, leads to recruitment of reduced populations of dendritic cells, reduces malondialdehyde in plasma, increases populations of CD4+ T cells of spleens, and increases the bioactivities of plasma SOD and CAT (Kang et al., 2016; Lee et al., 2015; Zhang et al., 2016). In vitro studies have also shown that resveratrol stimulates apoptosis in the HaCaT keratinocyte cell line. Hence, the intake of dietary phytochemicals is a promising candidature for the treatment of psoriasis.
### 7.4 Dietary phytochemicals attenuate RA

RA is a systemic, chronic autoimmune joint disease that affects 1% of the general population, primarily women rather than men (Skoczylis & Świerkot, 2018; Sung et al., 2019). This disease generally affects the quality of life with increased morbidity and decreased life expectancy. Numerous factors, including genetic, hormonal, environmental, and immunological factors, may contribute to the pathogenesis of the disease (Smolen et al., 2016). The pathology of the disease is characterized by synovial inflammation of multiple joints, swelling, and the production of autoantibodies that lead to the destruction of cartilage and bone. During the course of inflammation, there is a discharge in inflammatory mediators and proteolytic enzymes and a generation of ROS that contribute to the deterioration of clinical symptoms. These worsening signs in the organs lead to systemic features such as cardiovascular, pulmonary, and skeletal disorders, with augmentation of morbidity and mortality (Mellado, 2015). The cascade mechanisms of the immune response contribute to the decreasing immunological tolerance of B and T cells against autoantigens, with an ensuing autoimmune response in the joints (Scott et al., 2010). T cells activation generally triggers macrophages in the joints that stimulate angiogenesis, secretion of protease, the proliferation of fibroblasts, recruitment of leukocytes and lymphocytes, and specific expression of cell-adhesive molecules such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion protein 1 that contribute to the inflammatory destruction of cartilage and bone (Mellado, 2015; Navegantes et al., 2017). Many cytokines such as IL-1, IL-6, IL-12, IL-21, IL-23, and IFN-γ and elevated levels of cyclooxygenase-2, NO synthase, metalloproteinase, and other proteinases promote synovial inflammation and cartilage and bone destruction (Brzustewicz & Bryl, 2015; Makol & Krause, 2016; Tanaka et al., 2014). Another noteworthy mechanism of the inflammatory process in RA is the elevation of ROS production, acting as immunological mediators. ROS are often involved in the prevention of proteoglycan synthesis and degradation of the bone cartilage that may trigger the p53 gene mutation in synovial tissues (Engler et al., 2015; Quiñonez-Flores et al., 2016).

Dietary phytochemicals such as resveratrol, EGCG, naringenin, quercetin, silibinin, kaempferol, and curcumin are promising dietary substances that reduce joint inflammation and cartilage damage: decrease synovitis with pannus development; reduce inflammatory cell infiltration in the knee and bone; reduce expression of TNF-α, IL-6, and IL-1β in serum; reduce levels of IL-17, chemokine (C-C motif) ligand 20, and retinoic acid-related orphan receptor gamma in lymph node cells; and reduce expression of CD4+, IL-17, phospho-signal transducer and activator of transcription 3+, and Src+ splenic T-cells. Also, these dietary phytochemicals decrease ROS and inflammatory markers and block p38 gene expression and c-Jun N-terminal kinases pathways (Glehr et al., 2013; Haleagrahara et al., 2017; Lee, Moon, et al., 2018; Lee, Woo, et al., 2018; Li et al., 2015; Min et al., 2015; Tong et al., 2018). Hence, a regular intake of dietary phytochemicals could reduce the effects of RA and its complications.

### 7.5 Dietary phytochemicals attenuate ALS

ALS is a serious neurodegenerative disease that causes selective dysfunction of motor neurons of the spinal cord and brain stem (Figueira et al., 2017). The underlying mechanisms and pathogenesis of ALS are connected with ROS, mitochondrial dysfunction, and subsequent failure of the respiratory chain, which are the primary factors causing neurodegeneration (Carrera-Julía et al., 2020). There are generally two classifications of ALS, familial ALS, related to genetic inheritance, and sporadic ALS, connected to genetic and environmental factors. Both involved similar symptoms such as muscle weakness, which is often seen in the limbs, axial, bulbar, or respiratory muscles, and later may lead to paralysis, gradual disability, respiratory failure, and death (Caplliure-Llopis et al., 2019). This disease is mainly caused by a mutation in the TAR DNA-binding protein or a translocated liposarcoma protein that produces a high expression of TAR DNA-binding protein 43 with antioxidant enzymatic genes, SOD1. The high accumulation of SOD1 deals with the damage of mitochondria that elevates glutamate and cellular superoxide levels resulting in the formation of free radicals. This process triggers oxidative stress and causes cellular damage (Spaggiari et al., 2019).

Dietary phytochemicals such as morroniside, EGCG, madecassoside, and allin elevates cellular glutathione, activate phase II detoxifying HO-1 enzyme, and eventually reduce the release of ROS formation (Caló et al., 2010; Guo et al., 2011; Koh et al., 2006; Kou et al., 2011; Kumar et al., 2019; Wang et al., 2007, 2009). In addition, these natural antioxidant phytochemicals decrease lactate dehydrogenase and inhibit SOD activity that would usually maintain the stability of the cell and the mitochondrial membrane potential (Caló et al., 2010; Guo et al., 2011; Kou et al., 2011). These active compounds also downregulate Bax and caspase-3 expression and upregulate the expression of HO-1 and Bcl-2 through activation of extracellular signal-regulated kinase 1/2 and Akt-dependent signaling pathways (Kou et al., 2011). Finally, these natural dietary compounds protect motor neurons from degeneration and improve the life span.

### 7.6 Dietary phytochemicals attenuate SLE

SLE is a chronic, multiorgan-associated AD, described by the generation of self-reacting antibodies and immune complexes that cause primarily organ and tissue damage (Constantin et al., 2018; Lever et al., 2020). SLE has a range of multifaceted features that vary among individuals, stimulated by various factors including environmental factors (smoking, exposure to chemicals, drugs, diet, stress, and viral infections) and an inherited predisposition (Mok, 2003). Experimental studies show that susceptibility to the disease is 10 times higher in monoygotic twins than in dizygotic twins, which indicates a vital epigenetic role in the onset of the pathogenesis (Moulton, 2018). Its high severity is due to an unpredictable prognosis, including the potential for swift organ damage. Studies show that patients with deficits in primary complement components, particularly C1q, C2, and C4, are at
the highest risk for the development of SLE (Looney et al., 2006; Rahman & Isenberg, 2008). Studies have revealed that the autoimmune response could be triggered by an augmented, abnormal apoptosis and decreased apoptotic cell clearance by macrophages elevating intracellular antigens, including anti-double-stranded DNA, in the cell. The occurrence of this anti-double-stranded DNA is common in SLE patients (Looney et al., 2006; Oliveira et al., 2017; Rahman & Isenberg, 2008). Overall, this process leads to an elevated immune response, with activation of T and B cells, and increased expression of IL-10 following the production of self-reacting antibodies. These high quantities of self-reacting antibodies provide the generation of an immune complex, which can eventually cause impairment in the cardiovascular system and renal system leading to death (Kahlenberg & Kaplan, 2013).

Naturally occurring dietary phytochemicals such as coumestrol, curcumin, resveratrol, and indole-3-carbinol have been described as improving the development of several diseases with their manifold bioactivities, including decreases in oxidative stress, inflammatory response, and apoptosis (Handono et al., 2015; Kurien et al., 2015; Schoenroth et al., 2004; Wang et al., 2014; Yan et al., 2009). These compounds have also been reported to ameliorate immune cell infiltration and to improve organ injury, reduce anti-autoimmune antibodies and pro-inflammatory cytokines release, and normalize Th17-cell differentiation (Kurien et al., 2015; Yan et al., 2009). Hence, these dietary phytochemicals may serve as auspicious candidates to attenuate SLE.

8  | PHENOLIC COMPOUNDS TARGETING INTESTINAL EPITHELIAL BARRIER DYSFUNCTION AND VARIOUS TYPES OF AD

In the present study, most of the phytochemicals are belonging to the classes of phenolic compounds, have the antioxidant capacity that affect Toll-like receptors and proteins of the nucleotide-binding oligomerization domain. This impact generally prevents epithelial cell binding and intestinal inflammation. Moreover, the antioxidant potential of phenolic compounds permits them to decrease the negative impacts of the ROS produced by the overstimulation of the immune system during AD. Polyphenols are pharmacologically dynamic with well-recognized immunomodulatory activity (Ganesan & Xu, 2017b; 2017d, 2017e, 2018a, 2018b; Xu et al., 2020). Nevertheless, the challenging key issues in evaluating their pharmacological activity are the structural diversity of the compounds and their bioavailability that are greatly varied among the classes of the compounds. Additionally, each type of phenolic compound targets different immune cells and, thus, activates a plethora of different intracellular signaling pathways that eventually maintain the host’s immune response. The modulation of numerous signaling pathways leads to changes in the expression of pro-inflammatory genes, cytokines, cyclooxygenase, lipoxygenase, phospholipase A₂, and inducible NO synthetase, which combine with their capacity to moderate the population and differentiation of specific immune cells. Hence, phenolic compounds have antioxidant and anti-inflammatory activities and regulate the inflammatory mechanism. To date, mainstream mechanistic studies have established in vitro cell cultures given their greater simplicity and reproducibility; however, they fail to recapitulate several glitches that are inherent to oral administration, bioavailability, and the intense secondary metabolism to which phenolic compounds are subjected.

9  | CONCLUSION AND FUTURE PROSPECTS

Dietary phytochemicals modulate the intestinal epithelial barrier by maintaining the composition of the gut microbiota, reducing pro-inflammatory markers, normalizing the host immune system, and regulating intracellular proteins. These compounds modulate the function of the epithelial barrier via the inhibition of multiple protein kinases, namely, PKC, PI3K/Akt, tyrosine kinase, MLCK, MAPK, and AMP-activated protein kinase. Similarly, phytochemicals attenuate the complications and effects of various ADs including T1DM, IBD, psoriasis, RA, ALS, and SLE. Dietary phytochemicals are antioxidants with the properties of anti-inflammatory effects that reduce pro-inflammatory cytokines and mucosal inflammation, thereby preventing AD. Several in vitro and in vivo studies have also validated dietary phytochemicals as potential drugs for various ADs. Based on the present comprehensive review, dietary phytochemicals are promising candidates for the treatment of intestinal epithelial barrier dysfunction and ADs. Dietary phytochemicals are potentially involved in attenuating the dysfunction of the intestinal epithelial barrier and AD; however, further investigations are greatly mandatory to identify the dose and the bioavailability of the individual phytochemicals, pharmacokinetics, structural relationships, cellular mechanisms, and clinical trials. The synergistic effects of phytochemicals in combination with conventional drugs must also be explored. The diverse and distinct prospects of each phytochemical should also be systematically validated.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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