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UTILIZING PIGS AS A MODEL FOR STUDYING INTESTINAL BARRIER FUNCTION – A REVIEW

Marek Pieszka[1♦], Kinga Szczepanik[1], Igor Łoniewski[2,3]

[1]Department of Animal Nutrition and Feed Sciences, National Research Institute of Animal Production, 32-083 Balice n. Kraków, Poland
[2]Sanprobi sp. z o.o. sp. k., Kurza Stopka 5/C, 70-535 Szczecin, Poland
[3]Department of Biochemical Science, Pomeranian Medical University in Szczecin, 71-460 Szczecin, Poland
♦Corresponding author: marek.pieszka@iz.edu.pl

Abstract

Intestinal permeability has been extensively studied, particularly in gastrointestinal diseases such as inflammatory bowel disease, food allergy, visceral disease, celiac disease, and Crohn's disease. These studies have established that changes in intestinal permeability contribute to the pathogenesis of many gastrointestinal and systemic diseases. While numerous works in the 20th century focused on this topic, it remains relevant for several reasons. Despite the development of new research techniques, it is still unclear whether changes in intestinal permeability are the primary mechanism initiating the disease process or if they occur secondary to an ongoing chronic inflammatory process. Investigating the possibility of stabilizing the intestinal barrier, thereby reducing its permeability preemptively to prevent damage and after the damage has occurred, may offer new therapeutic approaches. Increased intestinal permeability is believed to lead to reduced nutrient absorption, resulting in decreased immunity and production of digestive enzymes.

Key words: pig, intestinal barrier, intestinal absorption, permeability, tight junctions

The gastrointestinal tract of pigs and humans represents the largest surface area through which an organism interacts with the environment. This tract serves as a critical interface, allowing the absorption of nutrients while also protecting against potentially harmful substances from the external environment. It forms a delicate and highly selective barrier between the organism and the external environment, including the bloodstream. This barrier plays a dual role: it selectively absorbs nutrients while preventing the absorption of harmful substances and antigens. Selective intestinal permeability involves a complex interplay of immune mechanisms, such as surface immunoglobulins and mucosal lymphocytes, as well as nonimmune mechanisms that contribute to the formation of the intestinal barrier.

The epithelial intestinal barrier serves three primary functions: absorptive, protective, and immunological. The absorptive function involves transporting vital fluids, electrolytes, and nutrients across the intestinal wall. The protective function prevents the absorption of insoluble, potentially toxic, pathogenic, or immunogenic molecules. The immunological function, mainly mediated by secretory IgA, binds bacteria and other antigens, preventing them from contacting enterocytes.

Intestinal barrier dysfunction underlies gastrointestinal and systemic conditions such as food allergy, gastrointestinal infections, visceral disease, chronic inflammatory bowel disease, cystic fibrosis, rheumatoid arthritis, multiorgan trauma, alcoholism, and Crohn's disease (König et al., 2016). Possibilities for studying the intestinal barrier in humans are very limited and consist of measuring paracellular (Hildsen et al., 1996) and transcellular permeability or the content of specific markers in the blood and/or stool (Quigley, 2016; Schoultz and Keita, 2020). The methods used are not fully satisfactory and can only detect significant disturbances of the intestinal barrier permeability. Differentiation of pore, leak or unrestricted pathways failures is in practice not possible. These problems make it very difficult to study the mechanisms of action of substances that reduce intestinal permeability. Therefore, development of appropriate animal models is crucial for safe preclinical protocols in human-oriented biomedical research. These models should allow for verifying and acquiring new research information relevant to the human body. Recent publications have extensively elucidated the physiological, pathological, and diagnostic aspects of the intestinal barrier, as documented in seminal works by Horowitz et al. (2023), Schoultz and Keita (2020), and Moonwiriyakit et al. (2023). Notwithstanding, these comprehensive analyses notably omit discussion of the intriguing porcine model.

The pig is a valuable model animal in biomedical research due to its genome's close similarity to that of humans, with approximately 94% congruence. This genetic similarity means that pigs, like humans, can develop identical protein disorders and dysfunctions that lead to diseases such as inflammatory bowel disease, obesity, Parkinson's disease, and Alzheimer's disease.

Additionally, the internal organs, endocrine system, and gastrointestinal tract of pigs closely resemble those of humans (Dzięgiel et al., 2018). This review highlights the strengths and limitations of using porcine models to study intestinal permeability, absorption function, and intestinal dysfunction resulting from weaning stress and dietary changes.

Pig model in gastrointestinal research

Pig models provide valuable research insights into livestock, veterinary medicine, and biomedicine (Dzięgiel et al., 2018). Experimental models of the porcine intestine are crucial for studying physiology, nutrition, and disease. The gastrointestinal (GI) tract, with a surface area of approximately 400 m^2, acts as a vital barrier between the external and internal environments. It plays a key role in regulating the immune system and overall health (Turner, 2009; Helander and Fandriks, 2014). The gastrointestinal mucosa serves a complex function as a semi-permeable barrier. It allows for the absorption of nutrients and immune sensitivities while limiting the transport of potentially harmful antigens and microorganisms (Shifflett et al., 2004). Regulation of this seemingly "contradictory" task is accomplished by the interplay of structural components and molecular interactions on the intestinal mucosa, which are essential for maintaining intestinal integrity and immunohomeostasis (Romero et al., 2015). More than 85% of passive transport occurs via the paracellular pathway, highlighting the crucial role of tight junctions in maintaining proper intestinal functioning. These junctions, located on the microvilli and surrounding enterocytes in the intercellular spaces, contain channels through which nutrients are passively absorbed. The number, density, distribution, size, and electrical charge of tight junctions determine the quantity and quality of absorbed substances. Clinical conditions characterized by increased intestinal permeability are often referred to as leaky gut syndrome.

Permeable bowel model using the pig as an example

The pig's many fundamental anatomical, physiological, and nutritional similarities to humans make it a powerful translational model for studying human digestive biology and diseases such as irritable bowel disease, Crohn's disease, and ulcerative colitis (Rothkotter et al., 2002; Kirk, 2003; Ibrahim et al., 2006; Lunney, 2007; Bendixen et al., 2010; Swindle et al., 2016; Roura et al., 2016). Using a pig model for intestinal barrier research, it is important to carefully plan animal care and handling for optimal study design, as psychological, nutritional, and physiological stressors can significantly affect mucosal barrier function.

The mucosal surface of the intestine is lined with a single layer of columnar epithelial cells, forming the primary physiological barrier against bacteria and bacterial products while facilitating the selective absorption of electrolytes, water, and nutrients. These epithelial cells have high energy requirements, and loss of perfusion to the intestine during conditions such as acute enteritis can lead to the rapid collapse of the intestinal epithelial barrier and the onset of sepsis. Pigs, like humans, experience gastrointestinal disorders in response to physiological and pathophysiological stress, which can impact intestinal barrier function (Lambert, 2009; Moeser et al., 2017). Swine models of intestinal stress, such as early weaning stress and heat stress induced by physical and social stressors, and sudden dietary changes, can lead to marked impairment of intestinal barrier function (Perce et al., 2013). These models closely mimic the effects of acute stress on the human gastrointestinal tract (Gareau et al., 2009; Moeser et al., 2007). The pig's advanced state of health and its similarities in brain neuroanatomy to humans suggest that pigs may have similar higher centers associated with the interpretation of social and physical stress, further enhancing their suitability as a model for studying the effects of stress on the gut (Gieling et al., 2011; Ziegler and Blikslager, 2017). While these striking similarities provide a very effective model for studying gastrointestinal physiology and disease, the stress sensitivity of pigs means that studies on intestinal barrier function must be carefully designed to minimize the impact of handling stress on experimental results (Engelsmann et al., 2023).

Histological structure of the pig intestine

The small intestine (Figures 1–3) extends from the distal end of the pyloric canal to the ileocecal junction and consists of the duodenum, jejunum, and ileum. While there is no sharp boundary between the jejunum and ileum, there are noticeable differences. The jejunum is wider than the ileum and has a thicker wall due to the large and thick circular folds (valvulae conniventes) (Bass and Wershil, 2015). The mesentery becomes fattier the farther into the distal part of the intestine one goes. The wall of the small intestine consists of four main layers from the outside: serous membrane, outer muscularis, submucosa, and mucosa (Standring, 2019). The intestinal mucosa serves as a digestive organ and also fights pathogenic bacteria and protects against the entry of toxins. Its development begins in the early embryonic period and can renew itself throughout life (Yang et al., 2013; Standring, 2019). The intestinal mucosa is composed of glandular epithelium, lamina propria, and muscularis mucosae. It is highly vascularized and contains Kerckring's valves. The epithelium and lamina propria form intraluminal protrusions called villi (Lee, 1990; Petras, 2013). Villi, which protrude into the intestinal lumen, increase the absorption surface area. Their size and shape vary depending on the part of the intestine, with villi length decreasing closer to the distal parts of the intestine (Barwick, 1986; Lee, 1990; Petras, 2013).

Each villus is covered with epithelium and contains a core of connective tissue in the lamina propria, which includes a centrally located lacteal, arteriovenous capillary network, and inflammatory cell populations (Mosenthin, 1998; Campbell et al., 2019). Adjacent to the villi are columnar depressions that extend into the muscula-

ris mucosa, known as Lieberkühn's crypts. The lamina propria of the villus core is continuous with the lamina propria surrounding the crypts. The ratio of villus length to crypt length varies and depends on various factors, including diet or age (Mosenthin, 1998; Petras, 2013; Itza-Ortiz et al., 2019). Stem cells in the villi produce proliferating transitional cells that differentiate into four types of differentiated cells, including enterocytes (one type of lymphoid cell), and three types of secretory cell lines: enteroendocrine cells, goblet cells, and Paneth cells (Xiong et al., 2019). Paneth cells migrate to the base of the crypts, while enteroendocrine cells and goblet cells move to the apical part of the villi (Van Der Flier and Clevers, 2009).

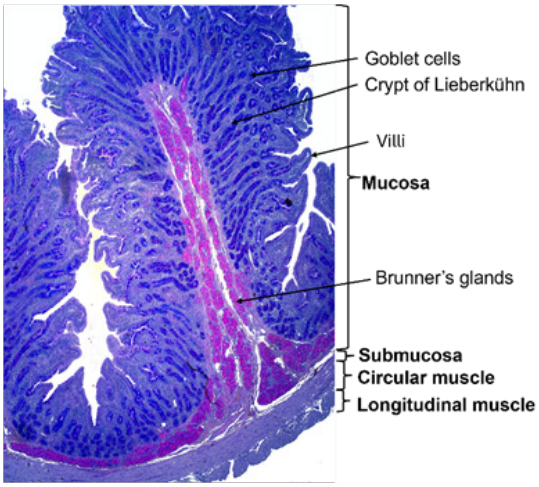

Figure 1. Representative microscopic photograph showing a section of the duodenum. Magnification 2.5×. Pas-Alcian staining

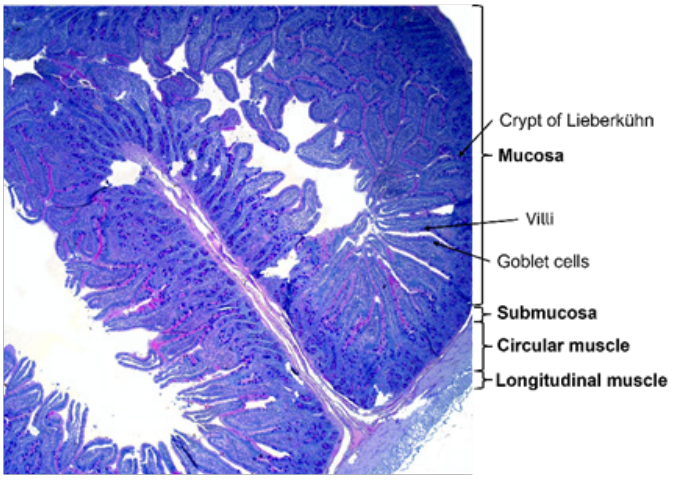

Figure 2. Representative microscopic photograph showing a section of the jejunum. Magnification 2.5×. Pas-Alcian staining

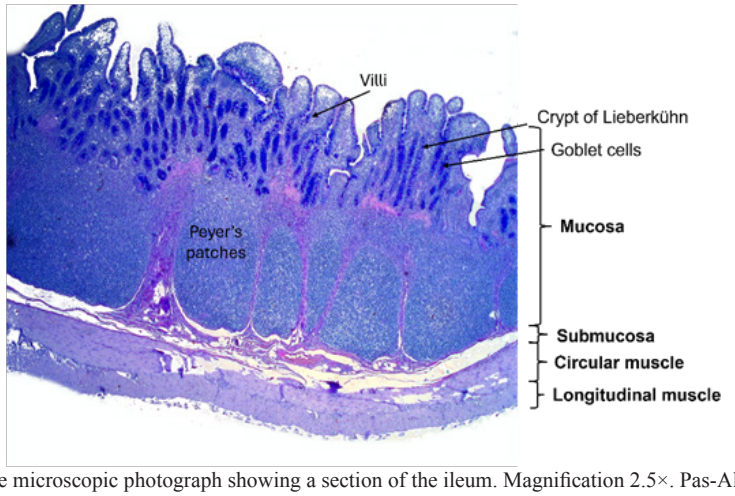

Figure 3. Representative microscopic photograph showing a section of the ileum. Magnification 2.5×. Pas-Alcian staining

The apical surface of the small intestine is covered with a brush border, which is ultrastructurally composed of microvilli and a glycocalyx or fuzzy coat (Petras, 2013). Goblet cells are scattered along the lining of the villi and are single-celled glands responsible for synthesizing and secreting mucins. The migration and differentiation leading to the excretion of goblet cells occur over a total of 2–4 days, with their numbers increasing in the distal direction of the intestine. Goblet cells also exhibit nonspecific endocytosis, whereby they endocytose soluble substances from the lumen and transmit antigens to antigen-presenting cells (Van Der Flier et al., 2009; Zhang and Wu, 2020).

The mucus of the small intestine covers the ends of the villi and fills the space between them, moved by peristaltic movements in the distal direction. It is constantly supplied from the cells of the villi, especially goblet cells from the orifices of the crypts (Schade et al., 1994; Ermund et al., 2013). The main component of intestinal mucus is the mucin MUC2, which is a glycoprotein with more than 80% of its molecular weight made up of glycans. The central part of the molecule is a protein backbone containing sequences rich in proline, threonine, and serine, which are highly O-glycosylated and constitute the mucin domains. The gel-forming mucin MUC2 oligomerizes into large, reticulated polymers when the COOH and NH2 ends form dimers and trimers stabilized by disulfide bonds (Ermund et al., 2013; Pelaseyed et al., 2014). The mucus secreted from the crypt is mixed with Paneth cell secretions, which contain antibacterial peptides, lysozyme, and DMBT1, among others. Paneth cell secretions and antibacterial proteins produced by enterocytes produce an antibacterial gradient in the mucus, making the epithelial cell surface virtually inaccessible to bacteria (Bevins, 2006; Pelaseyed et al., 2014). In the colon, the mucus exists as a hydrated polymer gel, 50–800 μm thick. Unlike in the small intestine, the colon's mucus consists of two layers: a loosely adherent layer and a layer permanently attached to the mucosa (Corazziari, 2009). Lymphatic enterocytes make up about 90% of cryptepithelial cells and more than 95% of villi cells. They are lymph cells with an apical microvilli membrane containing membrane-anchored transporters, receptors, and hydrolases.

The primary functions of enterocytes include nutrient digestion and absorption, as well as the formation of the intestinal barrier (Yang et al., 2013). Paneth cells, located at the base of the crypts in the small intestine, are highly specialized epithelial cells. As they mature and differentiate, Paneth cells migrate to the bottom of the crypts and accumulate numerous apical cytoplasmic granules (Porter et al., 2002). These mature cells are crucial for producing and secreting antimicrobial peptides, such as α-defensins/cryptidins, which play a physiological role in shaping the microbiome composition and maintaining gut homeostasis. Functionally and structurally, Paneth cells are involved in forming the stem cell zone of the small intestinal crypts and in the morphogenesis of the crypt-cell axis (Bevins and Salzman, 2011; Gassler, 2017). Endocrine cells are scattered as single cells in the mucosa, comprising approximately 1% of the cells lining the intestinal lumen. This cell population constitutes one of the largest endocrine systems in the body. Each endocrine cell secretes one or more hormones (such as gastrin, histamine, serotonin, cholecystokinin, somatostatin, and glucagon-like peptides) or hormone-like substances, which are released directly into the lamina propria and subsequently enter the capillaries (Rindi et al., 2004; Schonhoff et al., 2004; May and Kaestner, 2010). The lamina propria, which forms the connective tissue core of the villi and surrounds the epithelium of the crypts, consists of noncellular connective tissue elements (collagen and elastin), blood and lymphatic vessels, and myofibroblasts (Suvarna et al., 2013). The lamina propria is characterized by the presence of inflammatory cells, including plasma cells, lymphocytes, eosinophils, histiocytes, mast cells, and nerve endings. Plasma cells contain immunoglobulin (IgA or IgM) and are more concentrated in the intercryptic region (Mosenthin, 1998; Boudry et al., 2004). Histiocytes or macrophages usually cluster near the villi lumen and may act as antigen-presenting cells (Petras, 2013).

The submucosa, situated between the mucosa and the muscularis membrane, consists of loose connective tissue and fibroblasts. It contains inflammatory cells, blood vessels, lymphatic vessels, and nerve structures, including Meissner's plexuses, along with adipose tissue. The plexuses are composed of numerous Schwann cells, axons, dendrites, and glial-like cells (Boudry et al., 2004; Campbell et al., 2019). The muscularis mucosae, the outermost layer of the mucosa, is composed of elastic fibers and smooth muscle arranged in inner circular and outer longitudinal layers (Mosenthin, 1998; Petras, 2013). These smooth muscle layers are arranged as inner circular and outer longitudinal bands separated by Auerbach's muscular plexus. Blood vessels, nerves, and the lymphatic system pass through the muscularis propria (Boudry et al., 2004), which, along with Meissner's plexus, forms the enteric nervous system. This system regulates gastrointestinal motility by stimulating the muscles along the tract (Shahrestani and Das, 2024). A critical period in terms of intestinal histology is the peri-weaning period, during which changes in the histology and biochemistry of the small intestine, such as villous atrophy and crypt hypertrophy, are observed (Hampson, 1986; Pluske et al., 1997). This period disrupts the ratio of villi length to crypt depth, which stabilizes in the subsequent days of life (Pluske et al., 1997). An experiment by Wiese et al. (2003) showed that the villi of 7-week-old pigs are tongue-shaped. In the duodenum, they exhibit striations and are branched and undulating, while in the jejunum they resemble leaves with striations. In the ileum, at the sites of the lymphoid follicles, the surface appears jagged with curly, undulating villi. Crypts in the duodenum, jejunum, and ileum are mostly coiled and sometimes branched.

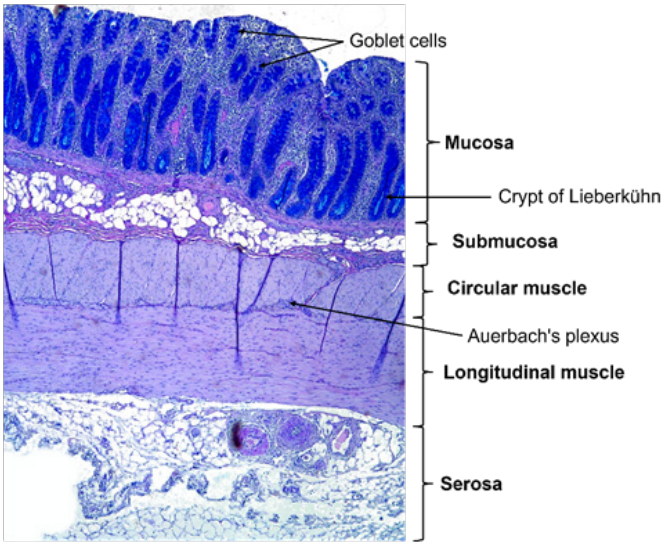

Figure 4. Representative microscopic photograph showing a section of the colon. Magnification 5×. Pas-Alcian staining

The duodenum is characterized by Brunner's glands, which start distally from the gastroduodenal junction and gradually decrease in size and distribution towards the distal end. In pigs, these glands can even be found, even discontinuously, in the jejunum. Brunner's glands contain scattered endocrine cells and Paneth cells (Krause, 2000; Accogli et al., 2018). Their secretions form a mucus layer primarily composed of mucin, which protects the mucosa from mechanical damage, neutralizes gastric juice acidity, modulates food content absorption, inhibits pathogen attack, and maintains bacterial microflora (Accogli et al., 2018; Zhu et al., 2021).

The jejunum is characterized by a higher villi to crypts ratio (Boudry et al., 2004). The ileum protrudes into the large bowel at the ileocecal valve. Its mucosa has fewer plicae circulares, more goblet cells, and shorter villi compared to the duodenum and jejunum. The ileum also has an increased amount of lymphoid tissue (Boudry et al., 2004; Petras, 2013). Scientific reports indicate that Peyer's tufts, clusters of lymphoid tissue, are present in both the jejunum and ileum of pigs (Chu and Liu, 1984). However, more T lymphocytes are found in the jejunum than in the ileum (Barman et al., 1996). Peyer's tufts in pigs begin to develop prenatally, between 76 and 91 days of the embryo, and undergo further development after birth, forming central, marginal, and subepithelial zones. Studies by Furukawa et al. (2020) have shown that Peyer's tufts in pigs after birth play a role in complementing the function of primary lymphoid tissue, promoting the differentiation and maturation of B lymphocytes.

The large intestine (Figure 4) marks the final segment of the digestive tract and is divided into three regions: the cecum, the colon, and the rectum. Unlike the small intestine, the large intestine lacks villi or circular folds. Nevertheless, its wall comprises four layers: the mucosa, submucosa, muscularis, and serosal membrane (Mosenthin, 1998). Similar to the small intestine, the mucosa of the large intestine includes glandular epithelium, lamina propria, and muscularis mucosae (Bass and Wershil, 2015).

Studies, including those by Brunsgaard (1997), have provided insights into the morphological characteristics of large intestine tissue in growing pigs. These studies have shown that early in a pig's life, there is a proliferation of crypts, known as crypt branching, which is an important process for tissue growth in the posterior intestine. Furthermore, significant changes in epithelial morphology and cell proliferation in porcine cecal and colonic tissue are most notable around the time of weaning. It has been observed that a greater proportion of mucins in the mid and distal colon are acidic or sulfated compared to the cecum, where mucins are predominantly neutral.

Intestinal barrier

The epithelial barriers of the gastrointestinal tract are selective and capable of excluding potentially harmful lumen contents such as gastric acid, toxins, bacteria, and bacterial antigens (Edelblum and Turner, 2009). At the same time, however, they have the ability to directionally absorb and secrete solutes and water. Substances pass through the epithelium through cell membranes, or the space between them, called the trans- and paracellular pathways, respectively (Chelakkot et al., 2018; Ma et al., 2018). The transcellular pathway is involved in the absorption and transport of nutrients. Specific transporters or channels located on the apical and basolateral membranes are involved in this process. The paracellular pathway, on the other hand, is associated with transport in the intercellular space between neighboring epithelial cells. The paracellular pathway involves apical connections: tight junctions (TJ) and adherens junctions (AJ) (Ferraris and Diamond, 1997; Chelakkot et al., 2018; Ma et al., 2018; Wang et al., 2019).

Apical adherens junctions (AJ)

Apical adherens junctions (AJ) are a feature of all epithelial layers (Fristrom, 1988). Together with desmosomes, they provide strong adhesion bonds between epithelial cells and promote cell-to-cell communication (Baum and Georgiou, 2011; Oda and Takeichi, 2011). While adherens junctions (AJs) and desmosomes do not directly seal the intercellular space within epithelial cells, they are essential for supplying the adhesive force necessary to maintain the integrity of the cell layer. Classic cadherins, alongside a group of transmembrane proteins, are pivotal components of adherens junctions (AJs). Cadherins, which are transmembrane proteins, consist of extracellular cadherin (EC) domains. Each cadherin comprises approximately 110 amino acid residues and possesses a cytoplasmic region that binds p120-catenin and β-catenin/pancreas at distinct sites. p120-catenin plays a role in stabilizing cadherins on cell membranes, while β-catenin/pancreas facilitates cadherin interactions with the actin cytoskeleton via α-catenin (Baum and Georgiou, 2011; Oda and Takeichi, 2011).

Tight junctions (TJ)

TJs surround the apical ends of lateral epithelial cell membranes and determine the selective paracellular permeability of solutes (Gasbarrini and Montalto, 1999; Tsukita et al., 2001; Ma et al., 2018). TJs are composed of four transmembrane regions with two extracellular domains and amino and carboxyl ends facing the cytoplasm (González-Mariscal et al., 2003). Both extracellular loops of claudins are similar in size, are very rich in tyrosine, and contain no charged residues. In the case of claudins, the first extracellular loop is longer than the second. Both claudin loops show a number of charged residues, which presumably affect the flow of ions through the paracellular space (González-Mariscal et al., 2003). Four integral transmembrane proteins were identified: occludin, claudin, junctional adhesion molecule (JAM), and tricellin (Furuse et al., 1993, 1998; Martìn-Padura et al., 1998; Ikenouchi et al., 2005). The intracellular domains of these transmembrane proteins interact with cytosolic scaffold proteins, which anchor the transmembrane proteins to the actin cytoskeleton (González-Mariscal et al., 2003; Barmeyer et al., 2015). This integration and cooperation of the TJ with the cytoskeleton enables the integrity of the epithelial barrier to be maintained. Occludin belongs to the integral proteins of the TJ. Its abundance is related to the degree of epithelial sealing (González-Mariscal et al., 2003). A surprising finding was the demonstration of the presence of tight junctions in embryoid bodies with the occludin gene knockout (Ocln) and the viability of Ocln knockout mice. This provided a basis for reducing the described role of this protein in epithelial barrier formation. However, Ocln knockout mice were observed to have numerous defects, including chronic gastritis, hearing loss, brain claudication, and male infertility. These problems can be linked to abnormalities and dysfunctions of the epithelial and endothelial barrier. This suggests that occludin is relevant to this area (McCarthy et al., 1996; Saitou et al., 2000; Kitajiri et al., 2014). Many signaling processes are involved in the regulation of occludin, including PKC and small GTPases and cytokines (McCarthy et al., 1996). Claudins are the main structural and functional elements of TJs and are characterized by distinct cargo selectivity, tightening the paracellular pathway or acting as paracellular channels, regulating ions and small molecules passing through the paracellular pathway. At least 24 members of the claudin family have been identified and most have been found to have charge selectivity (Van Itallie and Anderson, 2004; Barmeyer et al., 2015). According to current knowledge, the main functions of claudins include forming a barrier or channel ("fence function") and influencing cell signaling, proliferation, differentiation, receptor function, and migration. The third function consists of a "fence function" by which TJ restricts the mixing of lateral and apical membrane proteins (Barmeyer et al., 2015). The various claudins differ in their area of expression. For instance, claudin-2 and -15 are mainly expressed in the proximal parts of the gastrointestinal tract, while claudin-1 is expressed and localized primarily at the apex of epithelial cells. Claudin-2 is detected in both villi and crypt cells of the small intestine but is limited to undifferentiated crypt cells in the colon. Claudin-3, -4, -7, and -8 are primarily expressed in the distal parts of the gastrointestinal tract, specifically the colon, sigmoid colon, and rectum. Meanwhile, claudin-12 exhibits a ubiquitous expression pattern throughout the gastrointestinal tract. Claudin-4 and -7 are detected in both the lateral cell surface membrane and TJs. In contrast, claudin-5 is localized to the cell-cell boundaries of brain capillary endothelial cells (Morita et al., 1999; Oshima et al., 2008; Bertiaux-Vandaële et al., 2011; Lu et al., 2013). The incorporation and fusion of occludin, claudins, and JAM into tight junction strands require the localized clustering of scaffolding proteins. Among these crucial scaffolding proteins are zonula occludens proteins (ZO) such as ZO-1, ZO-2, and ZO-3 (Lu et al., 2013).

The intestinal epithelium functions as a barrier against harmful substances from the intestinal lumen, which largely depends on the integrity of the TJ. Therefore, damage to the TJ in the intestinal epithelium can disrupt the homeostasis not only of the gastrointestinal tract but also of the whole organism (Lee, 2015). During various intestinal and systemic diseases, intestinal permeability increases, i.e. the function of the intestinal barrier decreases (Horowitz et al., 2023).

Intestinal absorption of nutrients

Absorption of sugars

Sugars, including glucose, galactose, and fructose, are absorbed by the BBM of epithelial cells and then transported through the BLM by the facilitator transporter GLUT2 to enter the systemic circulation. The Na^+-dependent glucose/galactose co-transporter and the fa-

cilitator of fructose transport (GLUT5) are permanently located in the BBM to facilitate this goal when the luminal concentration of sugars is low between meals. However, this situation rapidly changes after food ingestion, when luminal glucose concentrations can reach several hundred millimeters (Pappenheimer, 1993).

In the rodent intestine *in vivo*, pharmacological knockdown of SGLT1 using florizine indicates that SGLT1 has a Michaelis constant (Km) of 20 mM and a maximum rate (Vmax) of 40 μmol·min^{-1}·g dry weight^{-1}, despite linearly increasing glucose uptake *in vivo* to >100 mM (Kellett and Helliwell, 2000). Therefore, after a meal, the luminal glucose concentration exceeds the capacity of SGLT1, and florizine only partially inhibits glucose uptake. Increasing evidence suggests the mobilization of GLUT2 to the BBM in response to increased glucose concentrations in the lumen to regulate glucose absorption, explaining the apparent diffusion kinetics of glucose absorption in the intestine (Kellett et al., 2008; Gorboulev et al., 2012). The expression of GLUT2 in the BBM of the intestine has been described by many independent laboratories worldwide, challenging the current understanding of glucose absorption. GLUT2 expression in the BBM in the intestine has been observed in response to glucose in enterocytic cell models (Zheng and Sarr, 2012), rodents (Scow et al., 2011), rodent models of diabetes, and obese patients (Ait-Omar et al., 2011).

Currently, two main views exist regarding the regulation of glucose absorption in the gut. The first suggests that glucose uptake solely involves SGLT1, with no expression of GLUT2 in the BBM (Shirazi-Beechey et al., 2011). The second view proposes that GLUT2 is rapidly and temporarily mobilized to the BBM from intracellular storage vesicles in response to increasing luminal glucose concentrations. This mobilization enhances the absorptive capacity of the intestine to match the nutrient load (Kellett et al., 2008). The translocation of GLUT2 to the BBM occurs within minutes, is temporary, and is recovered on a similar time scale in rodents. Evidence of GLUT2 expression in the BBM has been reported in insects, rodents, sheep, pigs, and humans, suggesting that this mechanism may be evolutionarily conserved, as discussed by Kellett et al. (2008). Very valuable results were obtained by Moonwiriyakit et al. (2018) who revealed the role of GPR40 in facilitating the epithelial connection of airways through the PLC-CaMKKβ-AMPK pathway. GPR40 represents an innovative regulator of respiratory epithelium integrity and its stimulation may be beneficial in the treatment of respiratory diseases.

Absorption of amino acids and peptides

The final products of protein digestion consist of a mixture of peptides and AA. Transporters on the BBM are conjugated with Na^+ or H^+, while dipeptides and tripeptides are transported by the BBM via an H^+-coupled peptide transporter called PepT1. For example, in the intestine, the uptake of glutamate and aspartate by the excitatory AA transporter 1 (EAAC-1) and peptides by PepT1 across the BBM are active processes coupled to the cotransport of Na^+ and H^+, respectively (Meredith, 2009). Inside the lymphatic epithelial cell, peptidases contribute to AA generation through peptide proteolysis. PepT1 substrate para transport to an electrochemical H^+ gradient through the BBM maintained by a Na^+–H^+ exchanger (NHE3), which itself is powered by sodium–potassium ATPase, which catalyzes the hydrolysis of ATP to ADP, in the BLM. EAAC-1 couples AA transport to an electrochemical Na^+ gradient maintained by Na^+K^+-ATPase. The dipeptides and AA exit the BLM through a series of carriers. To date, the molecular identity of the BLM peptide transporter (BPT) is unknown.

Although little is known about the regulation of EAAC-1 expression, it has been found to undergo mobilization to the membrane in C6 glioma cells to enhance glutamate transport (Fournier et al., 2004). In contrast, it is well established that PepT1 expression and mobilization are tightly controlled by dietary, hormonal, and protein kinase regulation (Adibi, 2003). PepT1 was the first nutrient transporter in the intestine to be regulated by BBM mobilization (Leibach and Ganapathy, 1996). This regulation has been demonstrated *in vitro* using Caco-2 cells and in the rodent small intestine, which endogenously expresses PepT1 (D'Souza et al., 2003; Mace et al., 2009). PepT1 expression in the BBM is negatively regulated by glucose, as an increase in glucose concentration *in vitro* decreases PepT1 expression and activity (D'Souza et al., 2003).

In addition, increased glucose concentration in the intestinal lumen has been shown to decrease PepT1 expression and dipeptide transport in the small intestine of rodents *in vivo* (Mace et al., 2009). This effect appears to be controlled, at least in part, by SGLT1, as BBM repolarization with chlorazine upregulates PepT1 expression. The expression of PepT1 and GLUT2 in the BBM seems to be mutually regulated (Mace et al., 2009). In contrast to the increased BBM expression of GLUT2 after streptozotocin (STZ)-induced diabetes in rats, PepT1 expression is completely abolished, revealing another link between glucose and peptide transport (Bikhazi et al., 2004).

Fats absorption

In brief, dietary fats enter the small intestine in the form of lipid droplets that are emulsified by bile acids and pancreatic secretions. Triacylglycerides are hydrolyzed by luminal lipase into fatty acids and monoglycerides for absorption across the intestinal mucosa (Hussain, 2014). Fatty acids and monoglycerides combine with bile acids to form micelles. As a result, fatty acids are present in the intestinal lumen as 4–8 nm particles within mixed lipid and bile acid globules, rather than as free fatty acids. Unlike the absorption of carbohydrates, peptides, and AA, micelles enter the lymphatic circulation as chylomicrons before entering the systemic circulation (Hussain, 2014).

Immunological function of the intestinal barrier

The immunological function of the intestinal barrier is mainly based on the secretion of secretory IgA. A decrease in the amount of secretory IgA increases the adhesion of bacteria to the intestinal epithelium, increasing intestinal permeability which, as a consequence, can cause bacterial translocation, that is, the penetration of pathogenic bacteria through the intestinal wall into the mesenteric lymph nodes or bloodstream. Undoubtedly, bacterial translocation is one of the mechanisms of post-traumatic multiple organ failure syndrome.

Both the immune and nonimmune components of the intestinal barrier are immature in the piglet. Hence, it is more susceptible to damage from toxic or infectious agents, but also more permeable as a consequence of exposure to allergens (cow's milk protein, soy protein; Loor and Herbein, 2001). The gradual maturation of the intestinal barrier is confirmed by the study of Kalach et al. (2001), who showed a decrease in intestinal permeability with age until about 3 months of age.

In the wild, weaning of pigs (wild boars) is a gradual process, almost complete at about 10–12 weeks of age, and coincides with the almost complete maturation of the epithelium of the digestive tract, immune system, and nervous system. However, in industrial pig production, weaning occurs suddenly between 14 and 30 days of age. An important stressor for piglets is the moment of weaning. Additional psychosocial and immunological stressors add to the stress during this period, including transportation, mixing, fighting and establishing a new social hierarchy, vaccinations, etc. The timing of commercial weaning also coincides with the period of disappearance of passive immunity derived from the sow's milk, which puts additional stress on the piglet. Weaned piglets can survive and overcome the stress of weaning, but it is important to note that early weaning stressors occur during a critical period of gut barrier development (Moeser et al., 2007). Many factors are known to directly or indirectly lead to an increased intestinal permeability. Undoubtedly, the most common among them are infectious factors (viruses, bacteria, and parasitic infections of the gastrointestinal tract). A study by Isolauri et al. (1995) showed an increased intestinal permeability among children with viral gastrointestinal infections. The increase in permeability was statistically greater among children who were "starved" during illness. Indirectly, through disruption of the physiological intestinal bacterial flora and overgrowth of pathological flora, antibiotic therapy can also lead to leaky gut syndrome. The mucosa of the gastrointestinal tract is continuously exposed to a wide variety of proinflammatory antigens. Under physiological conditions, only small amounts of these antigens penetrate the intestinal wall and activate local and systemic immunity. This response is carefully regulated and balanced with antigen exposure to maintain the integrity of the intestinal barrier and provide necessary protection.

However, excessive penetration of antigens or immune dysregulation can lead to an excessive immune response, which may result in gastrointestinal or systemic diseases (Romero et al., 2015).

Inflammatory bowel disease

In the course of inflammatory bowel disease, increased intestinal permeability is observed. This fact should not be surprising given the chronic inflammatory process, which is evident even macroscopically in the altered intestinal sections. This phenomenon has been confirmed by numerous clinical studies. The main question related to inflammatory bowel disease (IBD) and increased intestinal permeability is still whether increased intestinal permeability is a consequence of the inflammatory process or its causative factor. A study by Soderholm and Pedicord (2019) showed increased absorption in nondiseased sections of the intestine and increased susceptibility to damage stimulated by intestinal antigens of tight junctions, indicating a primary increase in intestinal permeability in patients with IBD. This finding appears to be supported by clinical studies that have shown increased intestinal permeability in close family members of IBD patients. However, whether this indicates a genetic predisposition to IBD associated with genetically determined higher intestinal permeability or the influence of environmental factors remains unclear.

There are differing opinions among researchers regarding the ability to predict relapse based on intestinal permeability assessment. Arnott et al. (2000) showed an increase in intestinal permeability preceding relapse, while Jørgensen and Elsborg (1996), based on their prospective study, confirmed increased intestinal permeability in Crohn's disease patients but ruled out increased intestinal permeability preceding relapse. It appears that the increase in intestinal permeability is secondary to the allergic process, as expressed by its increase after provocation with specific allergens in children with food allergies (Wasilewska et al., 2019). Undoubtedly, mast cells play a role in increasing intestinal permeability in individuals with food allergies upon allergen exposure. This was demonstrated by the use of disodium cromoglycate, a mast cell stabilizer, in these patients. Its use led to the normalization of permeability in allergic patients, and its prophylactic use did not increase intestinal permeability after allergen provocation.

Increased intestinal permeability is also observed in patients with visceral disease. The degree of its increase correlates with the degree of damage to the small intestinal mucosa, and the sensitivity of determining intestinal permeability in patients with visceral disease is determined to be 96%. It is suggested that this test can be used as a diagnostic method for screening and for tracking the progress of visceral disease treatment.

Diagnosis of intestinal permeability

Diagnosing intestinal permeability involves measuring the urinary concentration of ingested substances that have specific absorption characteristics and are not metabolized in the body. Substances such as Cr-51-labeled

EDTA, polyethyleneglycol, and others have been used for this purpose. For many years, researchers have predominantly used various nonmetabolized sugars. The sugar absorption test (SAT) is a well-established method for assessing intestinal permeability, where after oral ingestion of sugar samples, their levels are measured in urine. The limited number of papers on intestinal permeability is attributed to the requirement for expensive laboratory methods like gas chromatography or HPLC to assess the concentration of sugars in urine (Sequeira et al., 2022).

A combination of monosaccharides and oligosaccharides can help assess both the severity and location of intestinal damage. The most commonly used mixture includes mannitol, lactulose, raffinose, and sucrose. Mannitol, an easily absorbed monosaccharide, is not metabolized in the body and is absorbed throughout the intestine via the transcellular route. Lactulose, a disaccharide composed of galactose and fructose, is readily absorbed via the extracellular route. Urinary mannitol levels assess the transcellular absorption route and the absorption surface area, while urinary lactulose levels assess the extracellular pathway and the quality of tight connections. Sucrose is used to evaluate upper gastrointestinal tract damage (stomach and duodenum) as it is metabolized later.

SAT results are expressed as the ratio of the percentage secretion of a given sugar to the percentage secretion of mannitol, which corrects for ingested dose errors and peristalsis rate, providing a result related to the intestinal absorption area (Kubica et al., 2012). The clinical utility of SAT determination led to the development of simple laboratory methods for measuring these sugars in urine. A spectrophotometric method using appropriate enzymes was developed by a research team led by Hessels et al. (2003), enhancing the noninvasiveness and safety of SAT in diagnosing the severity and location of gastrointestinal damage. Assessing intestinal health also involves determining the intestinal microbiota, typically done through fecal analyses. The presence of specific bacterial groups and levels of pathogenic bacteria indicating dysbiosis can indicate inflammation of the intestinal mucosa (Gresse et al., 2017).

Most of the data on protecting and preventing damage to the intestinal barrier comes from experimental work on animal intestines and cell cultures (Vancamelbeke and Vermeire, 2017). Glutamine, an amino acid present in significant amounts in the bloodstream, is the primary source of energy for small intestinal enterocytes. Despite its high content in the blood during active intestinal damage, its levels may be insufficient. Studies on glutamine supplementation have shown mixed results. Spaeth et al. (1993) enriched nutritional mixtures used in total parenteral nutrition with glutamine but did not achieve significant improvements in permeability scores (Kansagra et al., 2003). Conversely, Klimberg et al. (1990) enriched oral meals with glutamine and observed a significant improvement in intestinal healing. A study on piglets receiving glutamine in their diet confirmed its beneficial effects on intestinal health (Ji et al., 2019). In another study, piglets weaned after 21 days and given 0.5%, 1%, 2%, and 4% monosodium glutamate for 21 days showed a dose-dependent reduction in the incidence of diarrhea in the first week after weaning (Rezaei et al., 2013), suggesting that glutamine or glutamate may alleviate diarrhea. Further studies indicate that feeding glutamine or glutamate to piglets can improve their daily weight gain performance (Molino et al., 2012) and intestinal epithelial structure and function (Rezaei et al., 2013; Wang et al., 2014).

Short-chain fatty acids, including butyrate, acetic acid, and propionic acid, are colonocytes' main energy source (Fussel and McCalley, 1987; Den Besten et al., 2013). They are produced by bacterial fermentation of fiber in the intestines. Improved intestinal barrier function has been scientifically confirmed after the use of plantain seeds and oats (Samuelsen, 2000). Of note, SCFA analysis should be performed in both blood and stool which is not always feasible. The levels of metabolites found in feces depend on their production, absorption, utilization by different microorganisms, and the stool's transit time. It is believed that about 95% of short-chain fatty acids (SCFAs) created in the intestine are quickly absorbed, leaving only 5% to be expelled in the feces (Den Besten et al., 2013).

Given that numerous proinflammatory prostaglandins and leukotrienes play a role in the inflammatory response in the intestine, as in other parts of the body, it is expected that the use of omega-3 fatty acids should improve or reduce inflammation. This hypothesis is supported by studies involving patients with Crohn's disease who were treated with a diet enriched with these fatty acids (Marton et al., 2019).

Metabolic endotoxemia

Dysbiosis, i.e. a disruption in the composition and function of the microbiota, promotes a loss of integrity of the intestinal barrier. As a consequence, bacterial antigens and endotoxins released from bacterial walls, i.e. lipopolysaccharides (LPS), and other bacterial metabolites pass through the intestinal barrier into the portal circulation, liver, and systemic circulation. Endotoxaemia initiates chronic inflammation and induces many inflammatory processes in the human body leading to metabolic complications. The metabolic processes induced by the microbiota directly affect total body weight (Hasani et al., 2021). Particular attention should be paid to the consequences of metabolic endotoxemia in peripheral tissues, namely the formation of an inflammatory environment in visceral adipose tissue and the development of insulin resistance. The occurrence of endotoxaemia in individuals diagnosed with obesity and metabolic syndrome has been fairly well documented (Abenavoli et al., 2019). This process involves, among others, monocytes and macrophages that phagocytize intestinal lipopolysaccharides (LPS) and then migrate to peripheral tissues, inducing inflammation in these tissues and changes in adiponectin synthesis and the release of leptin and resistin. Chronic

microinflammation enhances insulin resistance in peripheral tissues, and promotes increased production of insulin and insulin-like growth factors (IGF-1 and IGF-2), which stimulate cell proliferation, induce apoptosis and affect the expression of cell cycle regulatory proteins (Li et al., 2023; Hartstra et al., 2015). LPS leads to chronic urogenital inflammation, adversely affects metabolism and induces, among other things, hepatic steatosis and insulin resistance. All of the above processes lead to the development and accumulation of adipose tissue. Endotoxaemia significantly affects metabolism and impairs energy consumption in the body, stimulating the development of adipose tissue (de Vos et al., 2022).

Possibilities for improving intestinal barrier function

The consumption of mono- and multistrain probiotics can affect the composition and function of intestinal bacteria, regulate the local immune response, and create antifree radical substances, which stabilize the intestinal barrier and accelerate healing (Łoniewski et al., 2023; Kaczmarczyk et al., 2022; Salminen et al., 1996). Acting as prebiotics, oligosaccharides found in honey, beer, onions, rice, and bananas indirectly increase the number of probiotic bacteria in the intestines and short-chain fatty acids, significantly improving intestinal barrier function and reducing intestinal permeability (Westerbeek et al., 2011; Bischoff et al., 2014). Postbiotics are also a very promising option for supporting the intestinal barrier (Ahmadi et al., 2020). Postbiotics are defined as preparations made from inanimate microorganisms and/or their components that provide health benefits to the host. These can include inactivated microbial cells, with or without their metabolites or cellular components, as long as these elements have demonstrated health advantages. However, purified microbial metabolites and vaccines do not qualify as postbiotics. It is important to note that postbiotics do not necessarily have to originate from probiotics; any inactivated microbial source can be considered, provided it is proven beneficial and safe for the intended host. These hosts may range from humans to animals such as pets and livestock. Unlike probiotics, the action of postbiotics is not confined to the gastrointestinal tract; they can be applied to various host surfaces like the oral cavity, skin, and urogenital tract but cannot be administered via injection. For a substance to be classified as a postbiotic, its safety and efficacy must be established for the specific target host and application (Salminen et al., 2021). The best-studied postbiotic is pasteurized *Akkermansia muciniphila* MucT, whose action mainly depends on the Amuc_1100 protein (Plovier et al., 2017), which activates Toll-like receptors 2 (TLR2) and improves intestinal barrier integrity as well as reduces the burden of pro-inflammatory lipopolysaccharide (Cani and Kanuf, 2021). Research into improving the functioning of the intestinal barrier and reducing its permeability is focused on both the latest scientific possibilities, such as EGF treatment, and dietary treatments. Jensen-Jarolim et al. (1998) showed that hot spices like paprika and cayenne pepper increase the permeability of intestinal cell cultures, while black pepper, green pepper, allspice, and nutmeg significantly reduce it. Bovine colostrum is another promising ingredient for alleviating inflammation of the intestinal epithelium. It contains numerous leukocytes (white blood cells) from the maternal circulation, including lymphocytes, monocytes, macrophages, and neutrophils, which protect infectious agents through cytokine secretion and phagocytosis. These cells also regulate the development of the immune system of the newborn. Bovine colostrum also contains growth factors like IGF-I and IGF-II, similar to human colostrum, which bind to specific receptors on gastrointestinal mucosal cells, promoting their proliferation and differentiation. These factors also modulate tight junctions between enterocytes, regulating the permeability of the intestinal epithelium (Bregeon et al., 2016).

In the most reliable model of prematurity in pigs, administration of colostrum resulted in improved intestinal structure and function, enhanced nutrient absorption, decreased levels of proinflammatory cytokines (IL-1 and IL-8) in the intestine, better weight gain, and faster brain development (Woliński et al., 2012). *In vitro* tests showed that adding bovine colostrum to bacterial cultures (including *Escherichia coli*, *Serratia marcescens*, and *Klebsiella pneumoniae*) inhibited their binding to epithelial cells of the HT295 line. The molecular mechanism of colostrum action, recently confirmed in newborn mice, involves sulfated EGF factor inhibiting the activity of TLR4 receptors on the surface of intestinal epithelial cells. These receptors bind bacterial LPS and activate inflammatory processes. By inactivating these receptors, colostrum attenuates apoptotic processes of enterocytes, promotes their proliferation, and inhibits the expression of inflammatory factors, protecting the intestinal epithelium and alleviating symptoms of necrotizing enterocolitis (Chassaing et al., 2014).

Bacterial infections are the predominant cause of diarrhea in pigs, with invasions by *E. coli* or Gram-positive pathogens of the *Clostridium* genus, and Gram-negative pathogens such as *Lawsonia*, *Salmonella*, and *Brachyspira* being commonly observed. Viral infections by coronaviruses and rotaviruses also contribute to diarrhea. Protozoan infections, mainly coccidia, can also induce intestinal inflammation (Laine et al., 2008; Vondruskova et al., 2010). Probiotics are commonly used for gastrointestinal inflammation and prevention, as they are recognized as the most effective method for improving gut microbiota and treating dysbiosis (Maguire and Maguire, 2019; Łoniewski et al., 2022). Probiotics are live microorganisms that, when administered in sufficient amounts, provide health benefits (Hill et al., 2014). Studies have shown that probiotics can improve intestinal permeability homeostasis (Krumbeck et al., 2018; Łoniewski et al., 2022) and reduce inflammation (Sanders et al., 2019). However, the full mechanism of probiotics' positive health effects has not been fully explored. Probiotics

mainly modulate the gut microbiota and produce many metabolites that confer health benefits (Gresse et al., 2017). An imbalance of the gut microbiota and its functions can lead to disruption of tight junctions, resulting in intestinal permeability (Plaza-Díaz et al., 2020). For example, endotoxins such as lipopolysaccharides and other microbial metabolites line the vascular walls of the circulatory system and enter internal organs, which can cause mild to severe health problems such as inflammation, gastrointestinal disorders, neurological diseases, and neurodegenerative diseases (Anderson et al., 2010).

Several plants contain natural substances that significantly impact the intestinal environment by modulating bacterial flora and affecting the structure of the intestinal cell membrane. Cloves, for example, are rich in essential oil (16–20%), tannins (12–22%), nitrogenous compounds (4.7–7%), fats (5–10%), ash (5–9%), and crude fiber (6–10%), with wide therapeutic effects. Clove oil contains 70–90% eugenol (75–88%) and acetylugeol (4–15%), along with beta-caryophyllene (5–14%) (British Pharmacopoeia, 2009). Cloves inhibit putrefactive and fermentative processes in the intestines, stimulate and then inhibit gastric juice secretion, relax smooth muscles, provide analgesic effects in the gastrointestinal tract, and alleviate flatulence. They also have astringent effects on the gastrointestinal mucous membranes and exhibit antiparasitic, antibacterial, and antifungal effects (Cortés-Rojas et al., 2014).

Another noteworthy herbal ingredient is walnut leaves (*Juglands folium*), which are traditionally used in medicine for their antimicrobial, anthelmintic, astringent, antidiarrheal, and hypoglycemic effects (Taha and Al-Wadaan, 2011). Recent studies have shown that aqueous and ethanolic extracts of walnut leaves possess peripheral analgesic properties and are effective against acute and chronic inflammation (Holowacz et al., 2016). Walnut leaves contain gallotannin tannins (elagotannins and gallotannins) and 1,4,5-trihydroxynaphthalene-4-beta-D-glucoside, which transforms into a naphthoquinone derivative called juglon (5-hydroxy-1,4-naphthoquinone) during dying. The average content of tannins in the leaf is 4–5%. Additionally, walnut leaves contain flavonoids (quercetin and kaempferol derivatives, hyperoside), phenolacids (caffeic, p-coumaric), volatile oil (0.2 to 0.04%, containing about 40 different compounds, with 25% being sesquiterpenes), up to 1.3% ascorbic acid, carotenoids, triterpenes, and other compounds (Derebecka et al., 2012).

Conclusion

There is a growing interest in translational research involving large animal models, which enhances our understanding of the etiology and treatment of human diseases. Among these models, the pig stands out as particularly valuable for studying pathophysiological conditions relevant to the human gut. Several studies in recent years have emphasized that not only the correct experimental protocol but also the selection of an appropriate animal model can significantly influence the outcome and interpretation of the data obtained. With the increasing life expectancy of humans and the consequent rise in chronic diseases, gastrointestinal diseases, and neurodegenerative diseases, the importance of translational research in modern medicine is becoming more evident. Translational research using pig models holds promise for developing and implementing innovative solutions for public health. However, it is important to remember that no animal model perfectly replicates human biology and pathophysiology. Despite significant progress in translational medicine, numerous challenges and unanswered questions persist.

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