

Review article

CURRENT APPROACHES TO MODULATION OF INTESTINAL BARRIER FUNCTIONING IN PIGLETS: A LITERATURE REVIEW

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Abstract

The modulation of the intestinal barrier integrity in piglets during the early postnatal period is pivotal to the restriction of the propagation of enteric diseases agents, digestive efficiency, and performance. This review focuses on the primary morpho-functional changes occurring in the piglets' intestine after birth, including the development of the physical, chemical, and immune barriers. Critical stages in the maturation of intercellular adhesion and its role in keeping epithelial integrity are revised in detail. Particular stress is laid on the regulation of local immunity, including macrophage and dendritic cell involvement, secretory IgA production, and antimicrobial peptide synthesis. The mechanisms of interaction between intestinal microbiota and the immune system are discussed in respect of the stability of microbial community and adaptive immunity regulation. The roles of beneficial bacteria, including *Lactobacillus*, *Bifidobacterium*, and *Clostridia*, in infection resistance and intestinal epithelium metabolism are analyzed. Special emphasis is placed on the impact of weaning on intestinal barrier integrity, given that weaning stress is often accompanied by dysbiosis, disturbed microbial composition, and inflammation. Current approaches to keeping intestinal barrier functioning are reviewed, including the use of probiotics, prebiotics, synbiotics, exogenous enzymes, and antioxidant strategies. The efficacy of biologically active compounds, including short-chain and medium-chain fatty acids, polyphenols, and trace elements that strengthen intercellular junctions, modulate immune responses, and control inflammation, is discussed. The role of

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immunomodulators that activate local immunity, stimulate IgA production, and enhance antimicrobial defense is also considered. This comprehensive literature review highlights the mechanisms of intestinal barrier development in piglets, emphasizing its significance for animal health. The described data can be used to develop new strategies for managing piglet health and optimization of nutrition during weaning.

Keywords: piglets, weaning, intestines, microbial flora, cell communication, immunomodulation, probiotics, antioxidants.

INTRODUCTION

The development and maintenance of the intestinal barrier function is a key aspect of piglet health, resistance to infectious agents and productivity. In the early postnatal period, the intestinal barrier of newborns is immature, which increases the risk of pathogens translocation, the development of inflammatory processes and the impaired nutrient absorption. The weaning period is a crucial period for the maintenance of intestinal homeostasis. The principal change in diet induces an imbalance in the microbiota community and initiates the stress response in weaned piglets. The protective function of the gut is significantly provided by the main components, including physical, secretory and immune barriers. Their integrative interaction determines the effectiveness of the restriction in pathogens' invasion, the regulation of inflammatory response, and the metabolic status of the gut. One of the prospective approaches to maintaining intestinal barrier integrity is the use of immunomodulators, probiotics, prebiotics, short- and medium-chain fatty acids, antioxidants, and plant extracts. These biologically active compounds contribute to the strengthening of intercellular contacts, maintaining optimal microbiota composition, the reduction of oxidative stress and the improvement in local immune response.

This study aimed to analyze the mechanisms of the intestinal barrier regulation in early-aged piglets and to evaluate the efficacy of different approaches that can have a practical value for the increase in both gut health and animal productivity.

MATERIAL AND METHODS

The narrative literature review considers the analysis and generalization of current data regarding mechanisms of formation and modulation of the intestinal barrier function in early-aged piglets. The basis of the study was a critical analysis of peer-reviewed scientific articles, experimental studies, meta-analyses and reviews published in international databases, including PubMed, ScienceDirect, Springerlink, DOAJ, and Google Scholar for the period from 2000 to 2025. The following keywords and their combinations were used: "*piglets*", "*intestinal*

barrier”, “gut microbiota”, “weaning stress”, “probiotics”, “prebiotics”, “postbiotics”, “phytogenic feed additives”.

Several key criteria were used to include a study in the analysis. The inclusion criteria were applied: articles published in peer-reviewed journals; concerned the intestinal barrier integrity; highlighted methods of intestinal health maintenance; contained the results on feed additive supplementation in piglets growing; the reports on microbiome, intestinal epithelium, immunity interplays; concerned innovative approaches to preventing intestinal dysfunctions and modulating gut barrier functioning in piglets. Studies were excluded if they were: conference abstracts; non-English publications; works lacking full-text access or without scientific evidence (no references).

The primary selection was carried out based on both the titles and abstract content analysis. Data synthesis was carried out through qualitative analysis, highlighting key trends and effective approaches to the maintenance of intestinal health in piglets. Besides, the data systematization was constructed using content analysis, comparative analysis of research results and their critical evaluation. The obtained results provide the generalization of current knowledge concerning mechanisms of the intestinal barrier regulation in early-aged piglets and the formulation of a prospective line for further studies in this field.

RESULTS

The modulation of the intestinal barrier function in piglets in the early postnatal period is pivotal to their health and productivity. Understanding the mechanisms of barrier development and the impact of various factors may provide the opportunity to construct an effective strategy for maintenance of the intestinal integrity, which, in turn, contributes to the reduced incidence of diseases and better animal growth.

1. Morphological and functional features of piglet gut in early postnatal ontogenesis

The early postnatal period in piglets is characterized by intense morphological and functional changes in the gastrointestinal tract, which enables the vital process of adaptation to autonomous nutrition. Immediately after birth, the piglet gut is increasingly permeable, due to the immaturity of the epithelial layer and insufficient development of intercellular contacts. The intestinal barrier maturation is a multicomponent process, which includes epithelium differentiation, immune mechanisms promotion, and gradual colonization of the gut with commensal microorganisms. These adaptation changes play a crucial role in the formation of the intestinal barrier function, providing protection against pathogens and optimal nutrient absorption (Lallès et al., 2004).

Similarly to other mammals, the piglet's gut is anatomically divided into the small and large intestines. In newborn piglets, the former makes up approximately 5% of body mass. However, with animal age, this relationship decreases to 1.5%, resulting from the changes in the ratio of organs of the digestive system. The small intestine consists of the duodenum (5%), jejunum (90%), and ileum (5%). Each has specialized morphological and functional organization, which provides effective digestion and nutrients absorption (Lewis and Southern, 2000).

In newborn piglets, the length of the small intestine is approximately 2 m, and its capacity is about 72 ml (Marion et al., 2002). Before the weaning the length of small intestine increases more than three times, and its volume enlargement is more than nine times (Elefson et al., 2021; Wang et al., 2020). Although the surface area of the small intestine does not exceed 0,5 m² in newborn piglets, in 7-month-old animals it achieves about 6 m². This significant increase is dependent on the high nutritional value of the dairy diet, which does not leave a significant amount of undigested residues for fermentation in the large intestine (Greenwood-Van Meerveld et al., 2017). The development of the barrier function depends on the small intestine length, tight junction protein expression, cytokines production, and the morphology of villi and crypts (Dong et al., 2021).

The large intestine of newborn piglets is less differentiated than the small one. It also grows considerably slower (Weström et al., 2020). The length of large intestine reaches approximately 0.8 m, and its volume is about 40 ml (Chin et al., 2017). The large intestine increases in 1.5 times to three weeks of life while its development continues, even after the growth of the small intestine is completed (Elefson et al., 2021). The growth of the large intestine results from the gradual transition of piglets to more fibrous and less energy-rich feed, which stimulates the functional adaptation of the large intestine and the expansion of its enzymatic and absorption capabilities (Greenwood-Van Meerveld et al., 2017). A morphological feature of the pig's large intestine is the absence of villi in the mucosal layer. Meanwhile, it is coated with columnar epithelial cells with microvilli, which form straight tubular crypts. This provides epithelial layer renewal and mucus secretion (Chen et al., 2022). The caecum is relatively short in piglets, which reflects the special features of its digestive system (Wenk, 2001). After weaning, the large intestine grows until reaches 1.5% to 2.5% of the body mass (Hedemann and Knudsen, 2007; Wang et al., 2020; Yang et al., 2016). In adults, the large intestine length measures up to 7,5 m, and its volume 25 l (Barea et al., 2011; Elefson et al., 2021).

The formation of epithelial intercellular contacts in early-aged piglets is a critical mechanism that enables the functioning and the protective properties of the intestinal barrier. The immaturity of the intercellular adhesion in the first days of life promotes the absorption of immunoglobulins but also increases the risk of pathogen transmission (Wang et al., 2016). However, the gradual maturation of intercellular adhesion is controlled by hormonal, microbiological and nutritional

factors. It contributes to stabilizing the gut barrier integrity and controls its permeability (Masiuk et al., 2024a).

Intercellular contacts play a key role in the maturation of intestinal epithelial integrity, barrier regulation, and the selective permeability of piglets' guts in the early postnatal period (Guidoni et al., 2021). Epithelial cell contacts consist of several adhesive protein types, including tight junctions (TJs) and adherens junctions (AJs), which are formed in the first days of life and mature during postnatal development (Zhang et al., 2022).

The establishment of local immunity in the gastrointestinal tract of piglets is a multicomponent process, which includes the development of lymphoid structures, the activation of the mechanisms of cellular and humoral protection, and the interaction with intestinal microbiota (Wen et al., 2021). Piglet's gastrointestinal tract contains an extensive system of lymphoid tissue associated with the gut (GALT), which consists of Peyer's patches, intraepithelial lymphocytes, mesenteric lymph nodes, ileocolic lymph nodes, and lymph nodules in the small intestine (Jørgensen et al., 2022). The formation of all these structures begins in the middle of prenatal development. However, their functional activity depends on postnatal factors, particularly the communication with the intestinal microbiota. Moreover, milk diet components modulate the gut immunity potential.

Humoral immunity in piglets is provided by the colostrum and immunoglobulins of the sow's milk, including IgA, IgG and IgM in the early stages of development. IgA is the main secretory immunoglobulin, which forms immune complexes with pathogens and prevents their adhesion to the intestinal epithelium. IgG is transported across the epithelial barrier of the intestines and provides the systemic immune protection along with IgM antibodies, which participate in the primary immune response. The level of maternal immunoglobulins gradually decreases after weaning, which stimulates the immune system of piglets to synthesize their own antibodies.

Cellular immunity of the gastrointestinal tract is provided by T-lymphocytes, macrophages, and dendritic cells, which play a key role in the pathogen recognition, antigen presentation, and other events of adaptive immune system activation (Schäfer et al., 2022). Macrophages phagocytize microorganisms and produce proinflammatory cytokines, while dendritic cells are responsible for the activation of T-lymphocytes. The main subpopulations of T-lymphocytes differ in both functions and receptors CD4+ and CD8+. Together, these subpopulations regulate the inflammatory processes, the destruction of infected cells, and B-lymphocyte stimulation to produce specific immunoglobulins for long-term protection (Kumar et al., 2022; Maciag et al., 2022).

The postnatal colonization of the gut by microbiota is a crucial step in the development of local immunity (Kuthyar et al., 2023). Commensal bacteria, including *Lactobacillus*, *Bifidobacterium*, and *Clostridia*, are involved in the

regulation of pro-inflammatory and anti-inflammatory processes through the induction of T-regulatory cells, stimulation of IgA secretion and strengthening the intestinal barrier function by increased expression of molecules involved in intercellular contacts. Disbalance in intestinal microbiota is accompanied by various abnormalities including stress, chronic inflammation, increased epithelial permeability and high risk of infectious enteric diseases (Han et al, 2024).

2. Structural and functional organization of the intestinal barrier function

2.1. Physical barrier

The intestinal barrier not only provides selective absorption of nutrients, but is also of utmost importance in the protection against pathogenic microorganisms and toxins (Bao and Wu, 2021). Its structural and functional integrity is an essential feature that maintains homeostasis and reduces pathogens invasion into systemic blood circulation. The main components of the intestinal barrier are physical, secretory, and immune. The physical barrier consists of an intestinal single-layer epithelium, built of enterocytes, connected by tight intercellular contacts, such as TJs, AJs, junctional adhesion molecule (JAM), and desmosomes (Yang et al., 2022). These unique molecular structures provide the epithelial layer integrity, regulate paracellular permeability, and prevent the uncontrolled antigen and microorganism translocation.

The specialized junctions constructed by TJ and AJ proteins provide dynamic regulation depending on individual location and intestinal function, while AJs can trigger intracellular response and TJs structures are responsible for epithelial cell polarity and gut barrier integrity (Hartsock and Nelson, 2008).

TJs are the main structural components of the intestinal barrier, which regulate the paracellular transport and protect the epithelium from pathogen and toxin infiltration. The main proteins, which form these contacts, are claudins, occludin, and zonula occludens proteins (ZO-1, ZO-2, and ZO-3), which interact with the cytoskeletal components of epithelial cells (Chen et al., 2023). TJs are immature structures in the early postnatal life of piglets, which provides a high intestinal permeability in the first days of life. It enables the effective absorption of immunoglobulins from colostrum but also increases the risk of pathogen translocation across the epithelial layer (Inoue and Tsukahara, 2021).

Taking into the account the structure of epithelial cell junctions, occludin and claudins are key molecular markers of TJs and regulate the barrier functioning in the gut (Hartsock and Nelson, 2008). TJs impaired expression can lead to intestinal barrier dysfunction, particularly the development of “Leaky gut” syndrome, which is followed by increased epithelial permeability and chronic inflammatory processes.

Occludin, an integral protein of TJs, participates in the regulation of paracellular transport (Ballabh et al., 2004). Occludin can self-oligomerize or interact with other proteins to form an intercellular adhesion TJ type (Leong and Tong, 2015). Adequate occludin expression is important for intercellular adhesion, which provides the intestinal barrier integrity (Dubreuil, 2017). Claudins also play an essential role in paracellular transport and the regulation of intestinal permeability. A lack of claudin expression and the changes in its spatial distribution can disturb the barrier integrity (Fujita et al., 2006).

Formation and stabilization of TJs are regulated by several hormonal factors, including glucocorticoids and insulin-like growth factor-1. These hormones contribute to TJ protein expression and increase the number of intercellular contacts (Kurz and Seifert, 2021), stimulate colonization of the gut with microbiota, reduce the epithelium permeability (Lim et al., 2023), maintain the balance in protein and lipid nutrition, and minimize the risk of “Leaky gut” syndrome development (Zheng et al., 2024).

AJs are constructed by the association of cadherins (E-cadherin, N-cadherin), catenins (α -catenin, β -catenin), and actin filaments in complex structure, which provide both the strength of intracellular junctions and signaling from intercellular adhesion to intracellular pathways. In early-aged piglets, the adhesive junctions are not completely formed, which determines the increased sensitivity of the gut to both physical and microbial stress. The final maturation of AJs occurs during the first weeks of life and depends on: the mechanical load on gut during the feeding (Yuan et al., 2021); interaction with microbiota, which stimulates E-cadherin and β -catenin expression; the availability of essential amino acids (glutamine, arginine) that are substrates for the formation of cytoskeletal structures of enterocytes (Yin et al., 2022).

Extracellular matrix (ECM) proteins involved in cell-ECM adhesion and modulate physical barrier integrity through various mechanisms (Bontempo et al., 2026; Du et al. 2023; Masiuk et al., 2023a; Masiuk et al., 2024b). Fibronectin (FN) is a multifunctional glycoprotein of the ECM and plays an important role in cellular adhesion, proliferation and migration. FN enhances cell attachment and contributes to the repairing of damage via the interaction of epithelial cells with ECM (Kolachala et al., 2007). In case of malignant tumors, the level of fibronectin is significantly reduced, which indicates its role in the regulation of cellular metabolism (Rick et al., 2019). FN also interacts with collagen matrix and cytoskeletal components, contributing to the support of the tissue structure (Zollinger and Smith, 2017). Monoglyceride blend supplementation resulted in higher concentrations of FN in piglets after weaning, which evidences improved ECM and intestinal barrier (Masiuk et al., 2023b).

2.2. Secretory barrier

The secretory barrier consists of mucins, which form the protective mucosal layer of antimicrobial peptides and immunoglobulins, particularly secretory IgA. These components play a vital role in the pathogen neutralization, preventing their anchoring on the surface of enterocytes and their spreading in the intestinal mucosal layer. Mucins (MUCs) are specialized proteins produced by intestinal epithelial goblet cells, which are the main absorbance component of mucus (Tonetti et al., 2024). Mucin family consists of more than 20 proteins with minor differences in structure and function; in vertebrates MUC2 is predominant in the intestine (Arike and Hansson, 2016). A lack of MUC2 production leads to risk from enteric infections and pro-inflammatory changes, which highlights its importance in gut health (Tadesse et al., 2017).

Mucin content and its secretion are significantly increased in the early postnatal period, which contributes to the strength of the protective barrier (Chen et al., 2022). However, the mucosal layer is relatively thin in the small intestine, which provides the effective transport of nutrients and the interaction with microbiota. Meanwhile, the mucosal layer has one of most tight structure in the large intestine, thus providing the control of the microbial composition and prevent bacterial invasion into the deep layers of mucosa.

The mucosal layer plays a pivotal role in the protection of early-aged piglets' gut, creating physical, chemical and immune barrier between the intestinal content and enterocytes. Mucosal barrier is the first line of protection against pathogenic microorganisms, toxins, and mechanical damages. Furthermore, its structure provides a suitable microenvironment for the beneficial microbiota development (Yang et al., 2023). In newborn piglets, the mucosal barrier structures and their functions are not completely formed, which increases the risk of pathogen translocation across the intestinal epithelium.

2.3. Immune barrier

The immune barrier includes cells of innate and adaptive immunity, particularly macrophages, dendritic cells, and B- and T-lymphocytes, which are located in the lamina propria of the mucous membrane (Wiarda and Loving, 2022). These immune cells recognize and eliminate pathogens, and also modulate inflammatory processes and immune tolerance to commensal bacteria (Bemark et al., 2024). Thus, the intestinal barrier is a multicomponent system that provides physical, biochemical (mucosal), and immune protection. The components together maintain the balance between the nutrient absorption and the barrier function against pathogens (Figure 1).

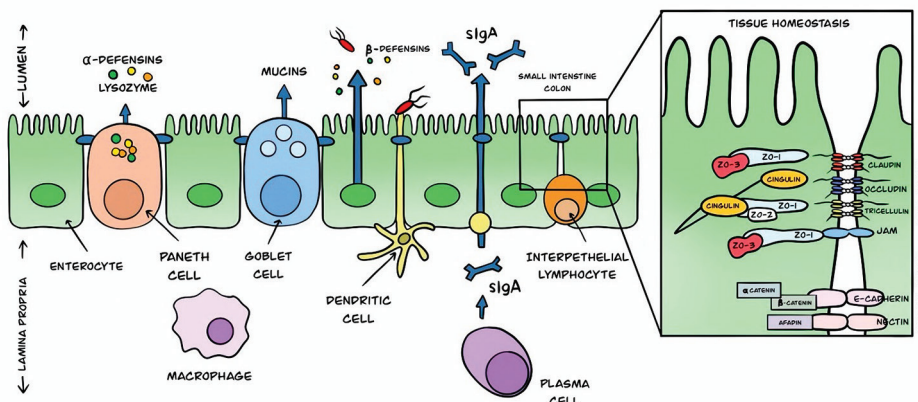


Figure 1. The main components of intestinal barrier in piglets. The physical barrier is constructed by TJ, AJ, and JAM proteins. Secretory (mucosal) barrier consists mucins, defensins, lysozyme, and antimicrobial peptides. Immune barrier consists of secretory IgA, dendritic cells, macrophages, and tissue-resident leukocytes.

Immediately after birth, colostrum consumption is the main means of protection against pathogens due to the unique composition, including high concentrations of immunoglobulins (IgA and IgG), mucins, antimicrobial peptides (defensins, lactoferrin, lysozyme) and a number of other biologically active molecules (Amatucci et al., 2022). Colostral antibodies serve as an “immune filter”, preventing the adhesion of pathogenic bacteria to the intestinal epithelium and neutralizing various antigens.

The intestinal system is the largest immune organ of pigs, given that almost 70% of all immunocompetent cells of the body are in the gut. It plays a key role in protection against pathogenic microorganisms, the regulation of inflammatory processes and support of immune homeostasis (Mörbe et al., 2021). Peyer’s patches contain T- and B-lymphocytes and perform the local immune control by providing antigen recognition and elimination.

Macrophages serve the function of first-line cellular protection in the piglet’s intestine (Yu et al., 2022). Located in the lamina propria of the mucous membrane, they are activated by pathogens’ penetration and/or damaged intestinal barrier integrity. Macrophages phagocytize pathogenic microorganisms, and produce anti-inflammatory and pro-inflammatory cytokines, which regulate the immune response (Li et al., 2023a). In the early postnatal period, the activity of macrophages is not completely developed. Therefore, the immune protection significantly depends on the factors that enter with colostrum. After weaning, the macrophage maturation is activated by metabolites of the intestinal microbiota and direct interaction with commensal bacteria (Tang et al., 2024).

Dendritic cells are the main intestinal antigen-presenting cells, which play an important role in the formation of adaptive immune response (Xia et al., 2022).

They permanently scan the intestinal content, engulf antigens, and transport them to mesenteric lymph nodes to activate immunocompetent T-lymphocytes. Thus, dendritic cells regulate the balance between immune tolerance to commensal bacteria and immune response to pathogens (Saha et al., 2024). In early-aged piglets these mechanisms are not fully developed, which explains their increased sensitivity to infectious agents, particularly during the weaning period (Yang et al., 2024).

Interferons are synthesized by various cell types and play a vital role in antiviral immunity, contributing to macrophage stimulation and the initiation of adaptive immune response. Intestinal macrophages and dendritic cells present antigens and provide the coordination of the immune response. The intestinal immune system is divided into inducible and effector sites. Inducible sites include mesenteric lymph nodes, where the primary activation and differentiation of the immune cells take place (Mowat and Agace, 2014). The effector sites are constructed of the intestinal epithelium, lamina propria, and the stroma of exocrine glands. Their interaction is important for barrier integrity as well as other protective mechanisms against pathogens (Brandtzaeg et al., 2008).

Cytokines are involved in various regulations, including intestinal immunity. Cytokines of the interferon family (IFN) play a central role in antiviral immunity and modulate other immune mechanisms in the gut (Van Winkle et al., 2020). There are three main types of interferons: IFN type I (IFN- α/β), IFN type II (IFN- γ) and IFN type III (IFN- λ) (Mesev et al., 2019). IFN- α/β and IFN- λ are the main mediators of early antiviral response, which contribute to the activation of immune cells and induce the antiviral state in tissues (Ye et al., 2019). IFN- λ receptor is crucial for the protection of the intestinal epithelial barrier by providing the antiviral effect with restricted inflammatory reactivity, which contributes to the maintenance of intestinal homeostasis during viral infections (Casazza and Lazear, 2019).

The balance between cell proliferation and cell death is important for homeostasis. Apoptosis is a widely occurring programmed cell death in all cell types. Caspases are cysteine proteinases that play an important role in apoptotic regulation and inflammatory processes (Brown et al., 2015). Caspase-3 (Casp-3) is a central effector enzyme in the cascade of apoptosis, responsible for the degradation of cellular proteins and cell death initiation (Ghazavi et al., 2022). The caspase-dependent mechanism can be activated by two means that include both exogenic (FasL binding receptors and TNF- α) and endogenic (mitochondrial) factors. The caspases are initiated by DNA damage and/or oxidative stress products, while cytochrome C is released from the mitochondrial membranes, and other pro-apoptotic mitochondria-associated factors (Bax, Bak, Bcl-2, BH3-only), which eventually activate the apoptosis cascades in all vertebrates (Zakariah et al., 2022).

In early-aged piglets, the immune mechanisms, including secretory IgA, macrophages, and dendritic cells, maintain the function of the gut barrier as a part of the total barrier system (Chen et al., 2022). These components play a critical

role in preventing pathogen penetration, and support the microbial balance and the formation of immune tolerance (Ferret-Bernard and Le Huërou-Luron, 2020). The secretory IgA is a key humoral component of local gut immunity (Erbs et al., 2025). Its production begins with the consumption of colostrum, which contains a high concentration of IgA that help to provide the primary passive protection of newborn piglets' intestinal mucosa (Raskova Kafkova et al., 2020). After weaning, the synthesis of IgA is activated by specialized B-lymphocytes located in Peyer's patches and mesenteric lymph nodes (Van der Weken et al., 2021). Secretory IgA builds immune complexes with antigens, preventing their adhesion to gut epithelium, and contributes to neutralization of bacterial toxins.

Taking into account that disturbance in every barrier component can lead to corresponding gut function abnormality, the measurement of respective biomarker content and/or expression is a convenient means to assess intestinal health. Gut health biomarkers are particularly relevant due to current requirements for minimizing invasive sampling in animal health monitoring. The expression and location of the intestinal barrier molecular markers, particularly of adhesive proteins, cytokines, and proteases, are important to assess when discussing the intestinal functional integrity (Du et al., 2023). Monitoring the changes in expression levels enables the creation of effective strategies of the prevention and therapy of diseases concerning intestinal barrier dysfunction (Masiuk et al., 2024b). The prospective application of several molecular markers to assess intestinal barrier integrity and/or disturbance has been described in recent reports (Masiuk et al., 2025; Shatalov and Kirici, 2024; Bontempo et al., 2026).

All described mechanisms build a multicomponent barrier, while each factor can stimulate the others. Thus, orchestral functioning of the intestinal barrier depends on both structural and signaling mechanisms.

3. The current approaches to modulation of the intestinal barrier function in piglets

Given the critical importance of the intestinal barrier integrity for health and productivity of swine farming, different approaches to the maintainance of gut health were proposed in the post-antibiotic era. The use of probiotics, prebiotics and postbiotics, antioxidant strategies, biologically active substances and immunomodulators were assessed and confirmed to be the most promised and prospective.

3.1. Probiotics

Probiotics are live non-pathogenic microorganisms, which, when introduced in sufficient amount, contribute to the improvement of body health (Capurso,

2016). They are widely used to stabilize microbial balance in the gastrointestinal tract, prevent pathogen colonization and to ameliorate optimal intestinal barrier functioning. In the last decade, probiotics have been undoubtedly considered to be a prospective alternative to antibiotics in animal farming. The most widespread probiotics are *Bifidobacterium*, *Lactobacillus*, and certain species of *Enterococcus*, *Streptococcus* and *Bacillus*, which contribute to the support of the healthy intestinal microbiome. Their positive effect is realized through competitive pathogen inhibition, secretion of antimicrobial substances (bacteriocins, organic acids), stimulation of local immunity and improved digestion. The administration of probiotics to sows (during pregnancy and lactation) contributes to improving the animals' health and stimulates piglet development (Pereira et al., 2022). Recent data demonstrated that probiotic supplementation contributes to IgG production in the sows' blood and increases the IgM levels in blood and the ileum mucosa of piglets during weaning. The use of *Bacillus*-derived probiotics has shown a trophic effect on the ileum mucosal barrier and biofilm formation by probiotic bacteria in the large intestines of piglets (Konieczka et al., 2023).

Bifidobacterium is a type of Actinobacteria (earlier Actinomycetes) and is one of the first microorganisms that colonize the gut in newborn animals (Castillo Zuniga et al., 2024; Kavanova et al., 2025). This bacterium plays an important role in the stable microbiome formation, preventing dysbiosis, diarrhea and creating optimal conditions for the development of the immune system. *Bifidobacterium* also increases the tolerance to lactose, decreases cholesterol levels, modulates local immunity and the synthesis of beneficial metabolites (He et al., 2023). For example, dietary supplements containing *Bifidobacterium breve* YIT4064 given to pregnant immunized mice protected their offspring against rotavirus infection better than antiviral immunization alone (Yasui et al., 1995).

Lactobacillus species are lactic acid bacteria, which are gram-positive, rod-shaped, catalase-negative, non-spore-forming, facultatively anaerobic microorganisms. Their main feature is the synthesis of lactic acid, which can acidify the medium, inhibit the growth of pathogens and support the intestinal barrier function (Kavanova et al., 2025). Lactic acid bacteria are widely spread in food products, feed, plant-based substrates, animal and human body, and are one of the key symbionts of the intestinal microbial community (Castillo Zuniga et al., 2024). *Lactobacillus* species have been confirmed to be among the most important probiotic sources relevant to the development of intestinal microbiome. Many studies conducted on pigs have testified that the use of lactic acid bacteria improves productivity, enhances immunity, and reduces the risk of diarrhea (Azevedo et al., 2012; Liu et al., 2013; Mao et al., 2016). The administration of certain strains of *Lactobacillus casei* and *Lactobacillus plantarum* contributes to decreased risk of viral infections and minimizes harmful effects of pathogens (Huang et al., 2021).

Escherichia coli Nissle 1917 (EcN) is a unique gram-negative probiotic that demonstrates an antagonistic effect against a broad spectrum of enteric pathogens.

EcN can regulate the secretion of immune factors that increase immune response (Zhao et al., 2022). EcN administered *per os* to piglets has shown a considerable antiviral effect, improved gut functions and reduced the duration of diarrhea (Michael et al., 2021).

The segmented filamentous bacteria (SFB) are gram-positive microorganisms, related to *Clostridium spp.*; they colonize the apical surface of epithelial cells in the terminal ileum. They play a key role in the protection against enteric infections and contribute to the regulation of immune response, especially to the stimulation of T-helper activity (Th17-cells). SFB are also involved in the prevention of the progress of autoimmune diseases and can modulate the tolerance to food antigens (Flannigan and Denning, 2018).

3.2. Prebiotics

Prebiotics are biologically active substances extracted from probiotics. They are selectively metabolized by commensal microbiome and contribute to body health. They play a key role in supporting optimal microbial balance that stimulate the growth and the activity of probiotics (You et al., 2022). The main groups of prebiotics are functional oligosaccharides, polysaccharides and natural plant-based extracts (You et al., 2022). The main function of prebiotics is the stimulation of the proliferative and metabolic activity of beneficial bacteria in the gastrointestinal tract. The metabolites of these bacteria strengthen the intestinal barrier, prevent the colonization of pathogens, modulate the immune system, activate the synthesis of secretory IgA and cytokines, increase the antioxidant resistance, and decrease the oxidative stress level (Ringseis and Eder, 2022). Prebiotics can reduce the risk of enteric infections and are considered a prospective alternative to antibiotics in animal farming due to various effects including an increase in animal productivity, modulation of barrier integrity, and maintenance of gut functions. The dietary use of pectin-oligosaccharide, lentinan or lactose improves the intestinal microbiome, strengthens the intestinal barrier function, increases the immune response and growth of piglets, and reduces the incidence of diarrhea (Chen et al., 2017; Mao et al., 2017). β -glucan administered orally influenced positively the whole state of animals and contributed to decreased mortality from rotavirus-induced diarrhea (Chethan et al., 2017). The supplementation of milk oligosaccharides or short-chain galacto-oligosaccharide blend and long-chain fructo-oligosaccharides to the diet contributed to the modulation of large-intestinal microbiota content and the increase in immune response (Li et al., 2014).

3.4. Synbiotics

Synbiotics are combinations of probiotics and prebiotics, which positively influence the host, improving survival and the colonization of useful microorganisms in the gastrointestinal tract. They have combined probiotic and prebiotic properties, creating a synergistic effect that helps the survival of probiotics in the intestines (Swanson et al., 2020). The corresponding combination of these two components demonstrates a more pronounced effect. The obtained results demonstrate the prospects of the use of synbiotics as an effective remedy to maintain intestinal health and increase resistance to infections. It has been proven that the oral administration of short-chain galacto-oligosaccharides, long-chain fructo-oligosaccharides and *Bifidobacterium breve* (M-16V) contribute to the decrease in symptoms of rotavirus diarrhea in rats (Rigo-Adrover et al., 2018). The resulting effect of symbiotics has been shown better than that of separate probiotics or prebiotics.

3.5. Postbiotics

Postbiotics are described as “soluble factors secreted by live bacteria, or released after bacterial lysis” (Gurunathan et al., 2023). They are various compounds including microbial cell wall components, peptides, enzymes, organic acids, and their derivatives (Liang and Xing, 2023). The beneficial effects of postbiotics can be mediated by both direct and indirect mechanism. Anti-inflammatory effect of postbiotics considered as one of most promised to maintain gut health (Wang et al., 2024). Furthermore, postbiotics exhibit multiple antimicrobial effects without resistance initiation (Liang and Xing, 2023).

Short-chain fatty acids (SCFA) and monoglycerides contained SCFA have demonstrated as alternative to antibiotics supplementation in animal husbandry (Kovanda et al., 2023). Monoglycerides are capable of maintaining morphological features of intestinal structures and modulate the gut microbiota content. Recent results have showed that the administration of α -glycerol monolaurate to piglets (GML) in a dose of 1 g/kg contributed to the increase of the ratio of the villi height to the crypts depth in duodenum, and stimulated the proliferation of goblet cells (Cui et al., 2020). Furthermore, GML supplementation initiated an increase in the height of villi in the jejunum and ileum, while the depth of the crypts remained unchanged (Li et al., 2022).

Postbiotics containing bacterial and fungal cell wall components deserve special attention due to mild stimulation of gut barrier functioning. Recent results demonstrated that yeast-derived postbiotics improve gut health and reduce pathogen translocation in spite of the absence of intestinal morphological changes (Hung et al., 2025). However, detailed mechanisms of postbiotics on piglet intestine barriers remain unclear and further study is required to explore the impact of various probiotic application on gut barrier integrity and growth performance.

3.6. Plant-derived extracts

Plant-derived extracts are the ancient remedies and are widely used health improvement medicines. Not surprisingly, similar compounds are supplemented for humans and animals. Therefore, several plant-based extracts were confirmed to be beneficial feed additives for farm animals, including pigs. As a rule, derived extracts exhibit multiple effects on metabolic pathways, homeostasis maintenance, and cell functions. Current data confirmed that the biological activity of natural substances is a main cause of the efficacy of plant extracts. The biological activity of many plant compounds were studied, including resveratrol, ginsenosides, saponins, quercetin, loureirin, baicalin, ziyuglycoside II, and genipin. A recent study demonstrated that the effects of these chemicals targeted gut barrier mechanisms. They are capable of modulating intestinal microflora, improving digestion, decreasing inflammation, and supporting the optimal state of the intestinal mucosal barrier (Yang et al., 2024). The use of these plant-based chemicals is considered a prospective approach to boosting animal health and increasing productivity. Particularly, the addition of prebiotics either 20 g/kg of inulin, or 40 g/kg of dried sunchoke to the diet of piglets has been successfully used as feed supplement, improving the qualitative properties of meat (Grela et al., 2021). Despite the long-time use of plant-derived extracts in animal husbandry, the dosage and timing of piglet treatment remain a controversial issue.

3.7. Exogenous enzymes

The addition of exogenous enzymes to the diet results in more effective conversion of food in the small intestine, that ameliorates definite compounds availability for microbial fermentation. For instance, proteases and carbohydrases effectively cleave proteins resistant to endogenous secretory enzymes and viscous non-starched polysaccharides accordingly. Both of them reduce the digestive viscosity and improve the nutrients absorption (Kim et al., 2022; Valente Junior et al., 2024). The beneficial effect of exogenous enzymes on the intestine functioning has been confirmed in recent reports. The use of enzymatic supplements in feeding improves digestion, contributes to optimal utilization of nutrients and supports the balance of intestinal microbiota (Rao et al., 2023). The key aspects of their activity is the capability to decrease the viscosity of intestinal content, to prevent the anti-nutritional factors and to reduce the level of substrates that can contribute to the excessive development of pathogenic microflora (Long et al., 2021).

Given that enzymes' effect on the animal health and productivity is dependent on their potential to improve the gut functioning, enzymes supplementation could be beneficial when the conditions of maintenance are far from optimal (Rao et al., 2023). For instance, in cases of increased microbial load or insufficient feed level enzymatic supplements can substantially reduce the risk of intestinal dysfunction,

contributing to the strengthening of the intestinal barrier function and the improvement of general animal health (Liu et al., 2023).

In the last decade, significant progress in the study of enzymes application in pig farming was achieved. Among the most effective enzymes administered to pigs several main groups were reported: phytases, xylanases, beta-glucanases, proteases, amylases, lactases, and cellulases (Dziurva et al., 2023; Edison et al., 2022; Kim et al., 2022; Moita and Kim, 2022; Lee et al., 2019; Valente Junior et al., 2024; Zhu et al., 2022). However, some aspects of enzyme supplementation remain unclear, including dosage, mixing with other feed additives, and optimal timing of administration.

3.8. Antioxidant strategies that support intestinal barrier

Antioxidants have long been used to reduce various oxidative damages. The support of early-aged piglets intestinal barrier function significantly depends on the effective control of oxidative stress, which occurs as a result of intensive growth, alterations in the diet and influence of external stress factors, particularly weaning (Blavi et al., 2021; Zhang et al., 2015). Antioxidant strategies are destined for the decrease the level of reactive oxygen species, cellular homeostasis maintenance, and the increase in antioxidant defense system activity. One of the key mechanisms of antioxidant defense is the use of natural antioxidants, including vitamins and other biologically active compounds. Vitamin E (α -tocopherol) and vitamin C (ascorbic acid) play an important role in the stabilization of cell membranes of enterocytes (Orengo et al., 2021). Vitamin A contributes to the regeneration of intestinal epithelium and supports the expression of TJ proteins (Wu et al., 2023). Polyphenols, particularly quercetin, catechins of green tea, resveratrol, and curcumin exhibit powerful antioxidant effect and proinflammatory activity that modulate signaling pathways linked with oxidative stress, decrease the level of proinflammatory cytokines' production, and contribute to the strengthening of intercellular adhesion in the gut epithelial layer (Pistol et al., 2023).

Several microelements, especially selenium and zinc, play an important role in antioxidant strategies due to direct regulation of antioxidant enzymes' activity. Selenium, present in glutathione peroxidase, protects enterocytes from oxidative damage, and zinc stabilizes the structure of TJ proteins and contributes to the intestinal epithelium regeneration (Zhou et al., 2024).

Prebiotics and probiotics also take a part in the antioxidant defense of the gut, particularly certain strains of *Lactobacillus* and *Bifidobacterium* that produce enzymes, which neutralize the active forms of oxygen. Prebiotics, including fructo-oligosaccharides and galacto-oligosaccharides, contribute to the growth of useful microflora that supports the balance of antioxidant processes (Pang et al., 2022). SCFA play a special role in the support of barrier function, particularly butyrate

enhances the expression of antioxidant enzymes and the TJ proteins (Liu et al., 2021).

The transmission of antioxidant capability between the sow and its fetuses is realized through the axis gut-placenta, as demonstrated in a recent report. Dietary glycerol monolaurate (GML) application exhibited a protective effect in sows during pregnancy (Zhang et al., 2024). Monoglycerides, particularly GML, are recognized as a prospective feed additives capable of activating the antioxidant system in pigs. Another study has shown a significant increase in both IL-10 level and glutathione peroxidase activity in weaned piglets (Li et al., 2022). Furthermore, glycerol monolactate addition to the diet decreased the concentrations of malonic dialdehyde and hydrogen peroxide in the ileum of pigs and stimulated the activity of superoxide dismutase and catalase in both the small and large intestines, which reflects its potent antioxidant properties (Li et al., 2023a).

Given that current data evidence that the results of antioxidant supplementation can be modulated by various external factors, further research is required to optimize antioxidant-containing diets.

3.9. Modulation of intestinal barrier integrity in piglets by biologically active compounds

Biologically active compounds are various natural chemicals that exhibit multiple effects. They can modulate the intestinal barrier by integrative strengthening of the intercellular contacts, immune response, and microbiota balance, and reduction of inflammation. The main biologically active compounds, which have proven themselves successful in practice, are polyphenols (quercetin, resveratrol, catechins, curcumin), SCFA (butyrate, propionate, acetate), prebiotics (fructooligosaccharides, galactooligosaccharides, inulin), peptides (lactoferrin, immunoglobulins IgA, defensins, casein peptides), microelements (Zink, Selenium), and medium chain fatty acids (MCFA) (caprylic, capric, lauric acids). All of them contribute to strengthening the intestinal barrier in piglets, decreasing inflammatory processes and supporting microbiome balance.

Some of the most important biologically active compounds are polyphenols, which have potent antioxidant and proinflammatory properties (Mao et al., 2024). Quercetin, resveratrol, catechins, and curcumin contribute to the decrease in proinflammatory cytokines (IL-6, TNF- α), stimulate the expression of TJ proteins (occludin, claudins, ZO-1) and maintain the balance in enterocyte recycling (Pistol et al., 2023).

MCFA, including caprylic, capric, and lauric acids, exhibit antimicrobial properties, contribute to the balance of intestinal microflora, decrease the levels of pathogenic bacteria (*Escherichia coli*, *Clostridium spp.*) and strengthen the intestinal barrier function. Besides, the MCFA as energy substrates ameliorate gut morphology, stimulate growth, increase immunity and can be supplemented as a

prospective alternative to antibiotics (Dahmer et al., 2020; Hanczakowska et al., 2016). Recent results have shown the high bacteriostatic activity of MCFA against a wide spectrum of pathogens, including gram-positive and gram-negative bacteria, viruses, fungi, and protozoa (Kovanda et al., 2023; Jackman et al., 2020). During weaning, piglets are stressed, which worsens nutrient absorption and disturbs gut energy balance. MCFA applied to the diet improve digestion, lipid metabolism, and provide optimal development and growth of weaned piglets (Cui et al., 2022).

SCFA play a key role in the intestinal barrier functioning (Ślupecka-Ziemilska et al., 2022). Butyrate is the source of metabolic energy for enterocytes. Furthermore, butyrate stimulates the secretion of mucins by goblet cells, increases TJ proteins' expression, ameliorates intestinal barrier integrity, and decreases pathogens' invasion (Cui et al., 2020; Li et al., 2023b; Li et al., 2022; Thomas et al., 2020). The addition of GML to the sows' diet improves the digestibility of crude fat and stimulates the average daily gain of piglets during weaning (Li et al., 2023c). Besides, GML supplementation improves the digestibility of various nutrients, decreases the pro-inflammatory processes, reduces intestinal permeability, and stabilizes the microbiota community in weaned piglets (Wei et al., 2023).

The improvement of intestinal barrier functions by immunomodulators is accompanied by local immunity strengthening, improved intercellular adhesion, and reduced inflammatory process in piglets (Masiuk et al., 2025). The application of immunomodulators, including β -glucans, lipopolysaccharides, nucleotides, cytokines (IL-10, IFN- γ), probiotics, and plant-based extracts, has been confirmed to be prospective feed additives that stimulate innate immunity, ameliorate both secretory IgA and antimicrobial peptides production (Chang et al., 2023; Saha et al., 2024). The supplementation of piglets' diet with β -glucans improves the barrier integrity via enhanced TJ proteins' (occludin, claudin-1, ZO-1) expression and stimulation of macrophage activity.

Thus, immunomodulators are prospective instruments for maintaining the intestinal barrier in piglets, decreasing the risk of infectious diseases, modulating immune response and providing optimal gastrointestinal tract adaptation to weaning stress.

CONCLUSION

This data analysis proves that intestinal barrier modulation in piglets is multifactorial and includes physical, secretory, and immune barrier regulation. The maturation of intercellular junctions in the first weeks of life strengthens the physical barrier and restricts its permeability. Secretory barrier development is accompanied by increased production of mucins, defensins, antimicrobial peptides, and lysozyme. The immune barrier stimulation depends on communication with the gut microbiota.

Weaning is a critical period for gut functioning in piglets. It is accompanied by acute changes in diet, stress, and dysbiosis, which together can cause post-weaning diarrhea, inflammation, and the disruption of the intestinal barrier. Thus, current approaches to maintaining intestinal health include the use of probiotics, prebiotics, synbiotics, exogenous enzymes, antioxidant compounds, and immunomodulators. All these provide the intestinal barrier integrity, reduce inflammation, and boost the immune response.

New solutions for an integrated approach to intestinal barrier preservation are promising areas for future research. Further research should concentrate on diet optimization and genetic elements of the intestinal barrier functioning in addition to the use of recognized agents. When taken as a whole, the idea of intestinal barrier preservation serves as the cornerstone of the strategy for enhancing animal health and pig farming profitability.

Authors' contribution

DM conceived the concept, study framework and took part in literature data analysis, OS analyzed and grouped literature data, DM and OS equally contributed to the writing of the manuscript draft, VN was involved in conceptualization, proofreading, and final revisions.

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Ethical statement

This study did not involve experimental research on live animals. All procedures were conducted in accordance with applicable institutional and ethical standards. ARRIVE guidelines are not applicable to this study.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflict of interest regarding the present work.

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SAVREMENI PRISTUPI MODULACIJI FUNKCIJE INTESTINALNE BARIJERE KOD PRASADI: PREGLED LITERATURE

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Kratak sadržaj

Modulacija integriteta crevne barijere kod prasadi tokom ranog postnatalnog perioda ključna je za ograničavanje razmnožavanja uzročnika crevnih bolesti, održavanje efikasnosti varenja i obezbeđivanje performansi. Ovaj pregled se fokusira na primarne morfo-funkcionalne promene koje se dešavaju u crevima prasadi nakon rođenja, uključujući razvoj fizičkih, hemijskih i imunih barijera. Kritične faze u sazrevanju međucelijske adhezije i njena uloga u očuvanju integriteta epitela su detaljno razmotrene. Poseban naglasak je stavljen na regulaciju lokalnog imuniteta, uključujući učešće makrofaga i dendritskih ćelija, proizvodnju sekretornih IgA i sintezu antimikrobnih peptida. Mehanizmi interakcije između crevnog mikrobioma i imunog sistema razmotreni su u pogledu stabilnosti mikrobne zajednice i regulacije adaptivnog imuniteta. Analizirane se uloge korisnih bakterija, uključujući vrste rodova *Lactobacillus*, *Bifidobacterium* i *Clostridia*, u otpornosti na infekcije i metabolizam crevnog epitela. Poseban naglasak je stavljen na uticaj odbijanja prasadi na integritet crevne barijere, s obzirom na to da je stres kod odbijanja često praćen disbiozom, poremećajem mikrobnog sastava i zapaljenjem. Razmatrani se aktuelni pristupi održavanju funkcije crevne barijere, uključujući primenu probiotika, prebiotika, sinbiotika, egzogenih enzima i antioksidativnih strategija. Razmatrana je efikasnost biološki aktivnih jedinjenja, uključujući masne kiseline kratkog i srednje dugog lanca, polifenole i elemente u tragovima, koji jačaju međucelijske veze, modulišu imune odgovore i kontrolišu zapaljenje. Takođe je razmatrana uloga imunomodulatora koji aktiviraju lokalni imunitet, stimulišu proizvodnju IgA i poboljšavaju antimikrobnu odbranu. Ovaj sveobuhvatni pregled literature ističe mehanizme razvoja crevne barijere kod prasadi, naglašavajući njen značaj za zdravlje životinja. Opisani podaci mogu se koristiti za razvoj novih strategija za upravljanje zdravljem prasadi i optimizaciju ishrane tokom perioda odbijanja.

Ključne reči: prasadi, zalučenje, creva, mikrobna flora, ćelijska komunikacija, imunomodulacija, probiotici, antioksidansi.