Feed Additives as Immune-Boosting Factors in Swine Health

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Abstract

Modern swine production systems globally are evolving, and the swine industry should adapt to new circumstances that include reduced antibiotics usage, reduced environmental impact, enhanced welfare requirements, increased sustainability under the scope of climate change, as well as exclusion of formerly used substances in pig feed, such as zinc oxide. The role of novel feed additives in health and productivity of pigs is gaining increased interest, as a factor that can improve response to the health challenges that pigs are facing in intensive units. The immune system is the major tool in combating diseases and disorders of the pigs and the vaccination scheme is the key component of a disease prevention program on farm. However, novel feed additives supporting or boosting the immune system, either at the organ/system level or at the total adaptive immune system level, are gradually becoming significant parts of swine health management programs on farm. Critical points of such immune support with feed additives are the intestinal immune response and intestinal homeostasis of the newly weaned pigs, as well as the proper immune preparation of sows, for improved passive immunity through colostrum in piglets.

Previous research data suggested the beneficial effects of basic feed ingredients and nutrients (amino acids, fatty acids, carbohydrates, etc.), as well as vitamins and mineral complexes, on the proper development and function of pigs' immune system. Recent advances provide evidence that eubiotics such as phytogenic feed additives and respective products of botanical origin, as well as other feed additives (probiotics, prebiotics, enzymes, etc.), could have anti-inflammatory, antioxidative, or antibacterial effects, or/and can support an

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improved immune response after antigenic exposure. The present chapter will focus on recent data, developments, and modes of action of novel feed additives that can improve the immune response of pigs.

Keywords

Pigs · Weaning · Feed additives · Immune response · Immune system · Intestinal barrier · Phytogenics · Prebiotics · Probiotics · Antioxidants

1 The Immune System of the Pig and Intestinal Homeostasis

The immune system of the pig is the predominant defense mechanism against infectious and other agents. Basic aspects of the immune response are inflammation, and cellular and humoral response (Oswald et al. 2005). Briefly, after engagement of the immune system (e.g., after contact with an infectious agent) a first defense mechanism takes action. This mechanism includes the innate immune response with phagocytic cells and production of various cytokines, chemokines, and proteins that provide antimicrobial protection, recruit T-cells through the inflammatory process, and further activate the adaptive, or acquired, immune response. Part of the innate system are also the natural killer (NK) cells that present a dual function including an innate response to attack infectious-agent-infected cells and production of cytokines for assisting in the activation of acquired immunity (Gerner et al. 2009; Mair et al. 2014; Chase and Lunney 2019). Thus, NK cells and other parts of the innate immune system such as defensins (host defense peptides), complement system, toll-like receptors (TLRs), type I interferons (IFNs), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-8 (pro-inflammatory cytokines) defend against pathogens, control infection, and activate the cascade of events of inflammation and adaptive immunity response (Chase and Lunney 2019). As previously demonstrated, toll-like receptors (TLRs) act as pattern-recognition receptors binding microbial ligands present in the lumen and determine the host-immune defense reaction, immune cell recruitment, and induction of mucosal inflammation, aiming at the preservation of intestinal homeostasis (Aderem and Ulevitch 2000).

The adaptive immune system utilizes B-cells, T-cells, cytokines, and antibodies, in order to provide pathogen-specific memory for protection from subsequent infections with the same pathogen. Lymphocyte populations (B- and T-lymphocytes) and antibody production reach optimal functional capacity two to three weeks after the first exposure to the pathogen. Immunoglobulins (Igs) show differences among each type, therefore IgG is the predominant Ig class (>80%) in the serum and colostrum of the pig, whereas IgM accounts for approximately 5–10% of total Igs in serum and colostrum. On the other hand, IgA is considered as mucosal Ig for swine. Mucosa epithelial cells secrete IgA, which assists to neutralize microbes in the lumen of respiratory and gastrointestinal (GIT) tracts (Kaetzel 2014). T-cell subsets express certain polarizing cytokines, the interleukins (ILs) or IFNs, as the immune response matures. Furthermore, cell-mediated immunity includes antigen-presenting cells such as macrophages and dendritic cells that phagocytize and process antigens and then present these antigenic fragments bound to swine leukocyte antigen (SLA) molecules as they contact T-lymphocytes, while also release cytokines (Chase and Lunney 2019). Taken together interactions with macrophages, T-cells and B-cells determine the balance between immune activation and tolerance induction, affecting the mucosal immune system in the GIT and consequently the overall health status of the animals (Bouwens and Savelkoul 2019).

It should be pointed out that piglets have limited ability in terms of T- and B-cell responses during the first few weeks of life, since it takes weeks after birth before B- and T-cell areas are formed in the bronchus-associated lymphoid tissue (BALT); thus they are heavily reliant on innate immunity given the maturity of this system at that time period (Lalles et al. 2007; Humphrey et al. 2019). Moreover, TLR-induced antiviral responses of plasmacytoid dendritic cells are reduced at birth in pigs but develop to a full response within weeks after birth (Jamin et al. 2006). Taken together, the innate defense mechanisms that neither require previous exposure to antigen nor have an immunological "memory" provide a first almost immediate response to the infectious agent and control infection, while at the same time assist in the activation of the adaptive immune system. The latter has immunological "memory" and will produce antibody- and cell-mediated immune responses (Chase and Lunney 2019). However, according to Netea and Van der Meer (2017), the adaptive immune response and the innate immune system can adapt to previous infections and develop memory, thus providing better protection against the same or heterologous infection.

Significant parts of the immune defense system in pigs are the mucosal epithelium (e.g., intestinal and respiratory tract), the microbiome (intestinal microbial ecosystem), and the lymphoid system consisting of the lymph nodes, lymphoid follicles, tonsils, thymus, and spleen (Rothkötter 2009; Wilson and Obradovic 2015). Thus, the first line of defense includes epithelial cells (epithelial layer is rapidly regenerating once every two to three days in pigs), bactericidal fatty acids, normal flora, and the mucus layer that is continuously produced, as well as cells with phagocytic abilities such as granular leukocytes (neutrophils, basophils, mast cells, and eosinophils), and mononuclear phagocytes (circulating blood monocytes and tissue macrophages), providing a mucosal immune system underneath the mucus-covered epithelial cell layer (Uni et al. 2001; Kelly and Mulder 2012; Williams et al. 2015). Furthermore, macrophage-mediated immunity, the activation of aryl hydrocarbon receptor (AHR), and the heat-shock protein (HSP)70 chaperone gene expression are well connected with the modulation of gut-associated immune response (Bouwens and Savelkoul 2019). The mucosal immune system prevents the uptake of pathogens and coordinates immune response, functioning as a defense tool with innate and adaptive cells that are accumulated in, or in transit between, various mucosa-associated lymphoid tissues (MALT) (Bouwens and Savelkoul 2019). The Peyer's patches, mesenteric lymph node, solitary follicles in the intestine, and the tonsils are points of immune response initiation and are included in MALT (Bailey 2009). Each mucosal tissue has its own associated lymphoid tissue resulting in

NALT (nasal cavity), BALT (bronchus/lower airways), GENALT (urogenital tract), and GALT (gut; GIT) (Bouwens and Savelkoul 2019).

An optimal intestinal microbiota prevents colonization of the intestinal epithelium by pathogens and penetration of the gut barrier, modulates the gut-associated lymphoid tissue (GALT) and systemic immunity, and influences gastrointestinal development (Broom 2015). The intestinal microbiota is a dynamic and complex environment and the interactions between the immune system and nutritional signaling at the intestinal level play a significant role in proper immune function. Immune reactions are generated from microbiota signals that direct responses with effector T-cells against pathogens or, in the case of commensals, induce a state of tolerance via modulation of regulatory T-cells (Tregs) and release of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β; Bouwens and Savelkoul 2019). According to Gresse et al. (2017), weaning age alterations include a reduction in obligate anaerobic bacteria (e.g., *Clostridia* and *Bacteroidia*) and an increase in facultative anaerobic bacteria (e.g., *Enterobacteriaceae*), which translate to decreased microbial diversity and a pro-inflammatory state within the intestine. Factors such as nutrition and management/husbandry approaches have a significant role in the microbiota alterations. Previous studies have presented facts that suggest differences among microbial communities and intestinal immune responses among piglets raised with the sow or fed with milk replacers (Lewis et al. 2012). Moreover, the age of weaning and the contact with solid feed affect the microbiota significantly (Bian et al. 2016). Taken together, various findings suggest that weaning is a predominant event in pigs' life that has multiple effects on gastrointestinal function and immune response, including activation of pathways related to inflammatory responses; alterations in hormonal activity; reduction in gastric motility; reduced villous height; reduction in nutrient, fluid, and electrolyte absorption; and increased permeability to antigens and toxins (Gresse et al. 2017).

2 Challenges for the Immune System and Gastrointestinal Eubiosis of Pigs

As described in the previous part, the intestinal immune system provides protection along the intestinal tract and balances the host response to microflora alterations and intestinal pathogens (Humphrey et al. 2019). However, there are plenty of challenges for the intestinal integrity and homeostasis during all stages of pig production. Diet alterations and stressful conditions, the transfer between units, and mixing of animals are benchmarks during these stages, which could affect proper intestinal function. On the other hand, interactions between the sows, embryos, and suckling piglets affect the intestinal microbiota development in early life and the intestinal immune response. As reported by Everaert et al. (2017), interventions through the maternal diet or direct to piglets in the pre-weaning period may have a beneficial effect on intestinal structural and functional aspects. Such modulations of the intestinal microbiota of sows can affect bacterial populations of the suckling piglets' GIT due to their contact with sow's feces.

The evaluation of the underlying mechanisms associated with intestinal function and immunity during the weaning transition is critical since successful weaning transition can result to an improved final body weight (BW) and reduced production days in total (Tokach et al. 1992). Efforts during that period include provision of highly digestible diets that will assist piglets' transition from milk to solid feed. Findings demonstrated by Main et al. (2004) suggested that an improvement of increasing weaning age by 1 day between days 12 and 21 would result in an extra 0.93 kg of day 42 BW and up to 0.47% reduction in wean-to-finish mortality. On the other hand, a transient anorexia at weaning leads to compromised intestinal barrier function and localized inflammatory response, as well as to an increase of reactive oxygen species (ROS) (Humphrey et al. 2019). The absence of feed stimuli in the intestinal tract at weaning affects immune cells' activity and balance of cytokines, chemokines, and other immune markers (e.g., IL-4, IL-10, and IFN-γ), thus decrease IgA content in intestinal and mucosal tissues and alters intestinal microbiota (Anastasilakis et al. 2013; Demehri et al. 2013). Therefore, it is crucial to establish a steady feed intake at weaning and a smooth transition to solid feed, in order to avoid inflammatory responses at the intestinal level or disruption of the intestinal barrier function.

Challenges from various pathogens such as enterotoxigenic *Escherichia coli* affect the nitrogen flow to the distal ileum, as well as the intestinal structure (e.g., villous height) and intestinal pH, with respective consequences on nutrient digestion and absorption processes (Heo et al. 2009, 2010). Effects of bacterial toxins on mineral and water intestinal absorption can contribute to the induction of post-weaning diarrhea in piglets (Sun and Kim 2017). Parasitic infections such as *Ascaris suum* alone, as well as their possible interactions with enteric bacterial pathogens such as *Lawsonia intracellularis*, can also contribute as disrupting factors to the intestinal function (Boes et al. 2010; Tassis et al. 2022). Viral challenges at the intestinal level such as *Porcine deltacoronavirus*, leading to intestinal microbiota alterations toward dysbiosis conditions (Li et al. 2020a), as well as particular mycotoxins affecting the intestinal barrier integrity and function (e.g., deoxynivalenol or fumonisins), are significant factors that affect intestinal health (Bracarense et al. 2012). Furthermore, reactive oxygen species (ROS), nitric oxide, hydrogen peroxide, or thiobarbituric acid-reactive substances are increased after weaning, due to weaning and weaning-associated intestinal inflammation (Zhu et al. 2012; Wei et al. 2017). Such substances have been associated with overgrowth of *E. coli* populations, whereas they could also result in reduction of natural antioxidants such as vitamin E, thus affect intestinal immune status (Kim et al. 2016; Wei et al. 2017).

Taken together, it is obvious that a variety of infectious and non-infectious challenges affect immune response of pigs during their life (Fig. 1). Furthermore, the antibiotics usage in intensive pig production is also a significant factor adding up to the above-mentioned challenges to intestinal eubiosis. Recent legal requirements for reduction of antibiotics usage and the ban of ZnO in pig feeds create a novel

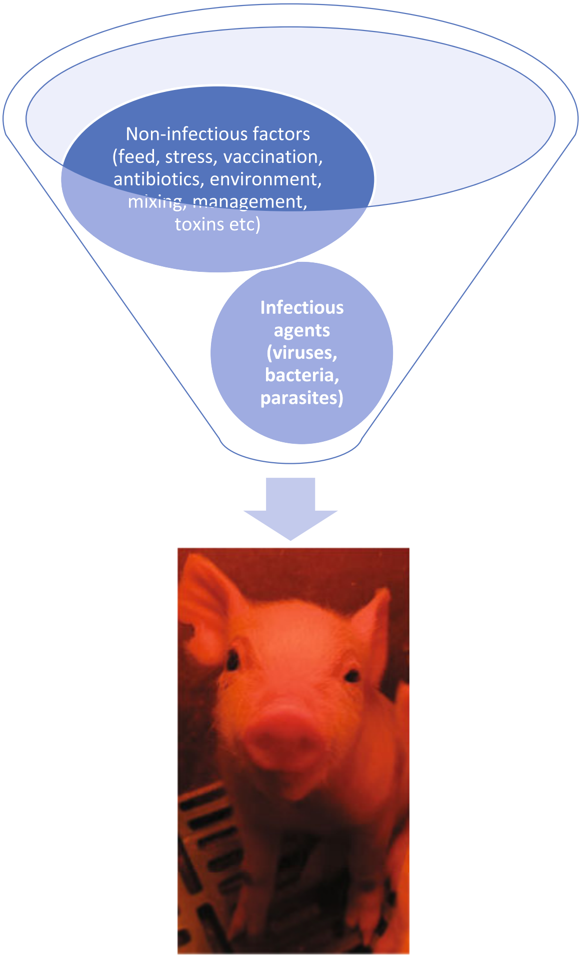

Fig. 1 Challenges for the immune system of the pig at weaning

environment for sustainable and welfare-friendly pig production. Therefore, the aim of optimizing gut health and immune responses is of major significance for the health and performance of the animals with reduced antibiotic usage.

3 Nutrition Interventions for the Improvement of Immune Response in Pigs

Nutritional interventions can affect the immune system at the intestinal as well as at the airways level in response to viral (e.g., porcine reproductive and respiratory syndrome virus) and bacterial (e.g., *Bordetella bronchiseptica*) infections, affecting pig health and performance (Opriessnig et al. 2011; Bouwens and Savelkoul 2019). Long-term overuse of antimicrobials in global pig production resulted in increased interest as regards the administration of alternative substances such as immunomodulators like cytokines, pharmaceuticals, microbial products, traditional medicinal plants, and nutraceuticals (Hardy et al. 2013; Bouwens and Savelkoul 2019).

According to the meta-analysis of Vanrolleghem et al. (2019), many studies have focused on potential dietary feed additives with antibacterial effects on weaned piglets, such as:

I. Antimicrobial peptides (small molecules [<10 kDa] with a broad-spectrum activity against bacteria, fungi, protozoa, and some viruses (Lai and Gallo 2009))
II. Chitosan (obtained from the shell water of industries processing crab, shrimp, and crawfish, with possible antimicrobial property (Singla and Chawla 2001))
III. Lysozyme (naturally occurring enzyme, with ability to cleave the glycosidic linkage of bacterial cell walls peptidoglycan (Ellison and Giehl 1991))
IV. Medium-chain fatty acids (MCFAs)/triglycerides (organic acids [OAs] with 6–12 carbon atoms acting as non-ionic surfactants, which are incorporated into the bacterial cell membrane (Desbois and Smith 2010))
V. Plant extracts and essential oils (with bacteriostatic and/or bactericidal and antioxidant effects (Franz et al. 2010))

The aforementioned analysis findings supported the possibility of antibiotics replacement with the above-mentioned feed additives, especially at the weaning period. In addition to those antibiotic alternatives, major interventions that could affect immune response and defense predominantly against intestinal pathogens, thus supporting eubiosis and proper intestinal function in pigs, will be demonstrated in the present chapter (Fig. 2).

4 Low-Protein Diets and Amino Acids Supplementation

Several studies have presented evidence between diets with increased protein levels and detrimental effects on the gut health of pigs, and a special relationship has been presented between feeding high levels of proteins and the incidence of post-weaning diarrhea in pigs, as reviewed by Rodrigues et al. (2022). On the other hand, it has been reported that diets with lower levels of proteins could improve gut health by suppressing the proliferation of pathogenic bacteria and increasing beneficial microbial populations (Wellock et al. 2008; Heo et al. 2009; Rist et al. 2013). Thus, since many years, a lower protein diet supplemented with crystalline amino acids (AAs) to meet requirements for essential AAs has been recommended, especially post-weaning, since through that intervention reduced undigested protein and harmful metabolites are available for the overgrowth of pathogenic bacteria populations in the gut lumen (Nyachoti et al. 2006). Nevertheless, it should be noted that additional factors, other than simply total dietary protein content, such as indigestible content,

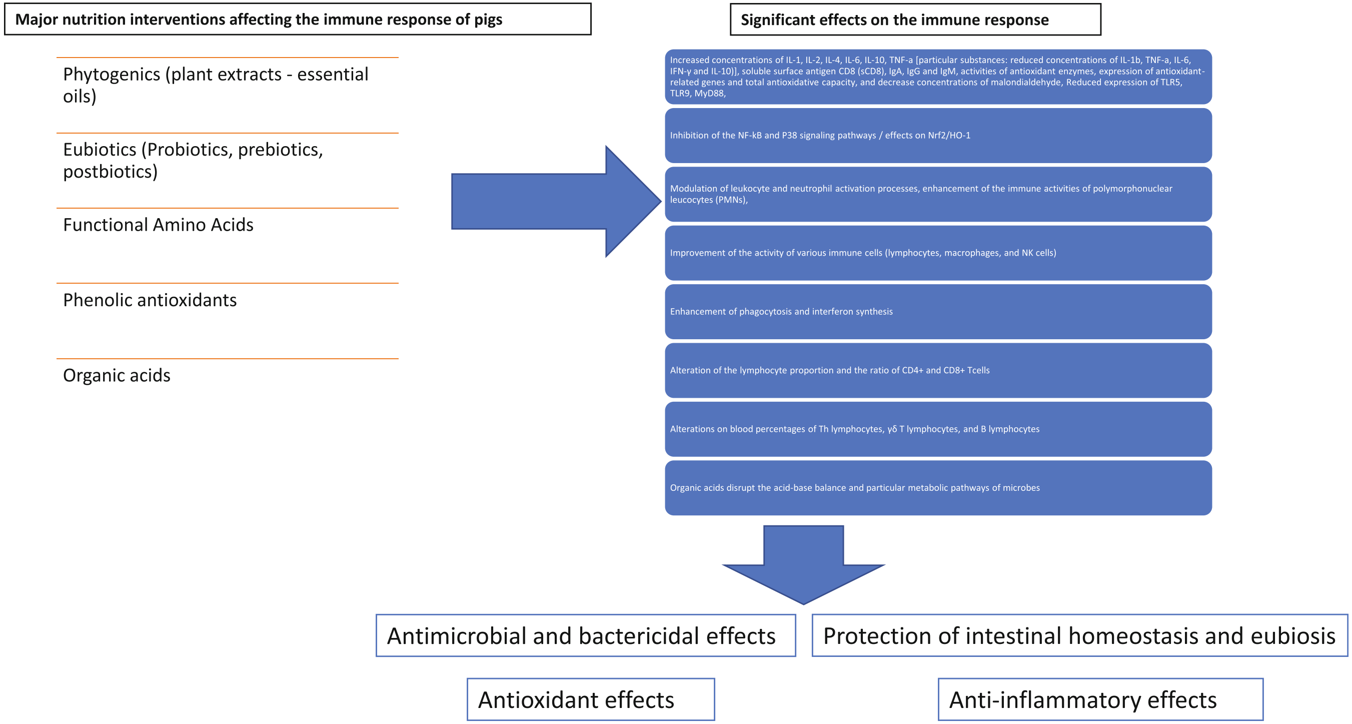

Fig. 2 Major groups of nutrition interventions and their mode of action that affects immune response of pigs

or protein type, could be also involved in the worsening of post-weaning diarrhea (Rodrigues et al. 2022).

A prioritization of AA utilization for the immune response at the expense of growth has been demonstrated (Reeds et al. 1994). It should be noted that a significant expenditure of AAs is present during inflammation, due to the need of AAs for endogenous antioxidants syntheses to cope with oxidative stress, as well as the necessity to support the activated immune system under such circumstances (Rodrigues et al. 2022). The circulating acute-phase proteins (e.g., C-reactive protein, serum amyloid A, haptoglobin, pig-major acute phase protein (MAP)) as well as the proliferation of immune cells (e.g., clonal lymphocyte and monocyte differentiation) and lymphoid tissue hyperplasia, along with the secretion of molecules such as cytokines and immunoglobulins by immune cells, are major points of AA expenditure during inflammation (Le Floc'h et al. 2004; Parra et al. 2006). Therefore, the AA needs in pigs are not stable and differ between physiological and inflammatory status. Evidence suggests a positive boost on immune response after AA supplementation, through the reduction of body protein loss and acceleration of recovery procedures (Le Floc'h et al. 2018). The "functional" roles of AAs beyond their role as constituents of lean gain are a major point of ongoing research.

As previously demonstrated, excess nitrogen available for fermentation in the distal ileum and colon can negatively affect the intestinal barrier function and immunity and contribute to post-weaning diarrhea at weaning (Kim et al. 2012). Tryptophan (Trp) has gained significant attention due to its metabolism to functional metabolites that possess immune regulatory properties (regulation of T-cell function and response) (Humphrey et al. 2019). Gao et al. (2018) reported that endogenous (kynurenine, serotonin, and melatonin) and bacterial (indole, indolic acid, skatole, and tryptamine) Trp metabolites can affect gut microbial composition and metabolism, immune response of the host, and host–microbiome interaction. Findings from other studies support the beneficial outcome of increased Trp intake in piglets, through the improvement of intestinal microbiome diversity, decreased abundance of opportunistic bacteria, and increased mucosal IL-8 mRNA level and zonula occludens (ZO)-1 (Liang et al. 2018). Based on a study by Wang et al. (2010), an optimal ratio of Trp:Lys of 0.89% for weanling piglets tofto support intestinal barrier function was concluded. Other amino acids of importance include glutamine, glutamate, proline, aspartate, ornithine, and citrulline. As regards lysine in nursery pigs, an average total lysine:crude protein (CP) ratio of 6.8% is often suggested (total Lys: CP ratio should not exceed 7.1%) (Nemechek et al. 2011; Humphrey et al. 2019).

Glutamic acid (GLU) is a non-essential amino acid, present in the body, which is a precursor of protein synthesis associated with cellular metabolism and immune responses. According to Kyoung et al. (2021), supplementation of weaners' diet with GLU provides benefits in terms of immune response and intestinal microbiota and function, since increased villus height to crypt depth ratio, number of goblet cells, and ileal gene expression of claudin family and occludin, and decreased serum TNF-α and IL-6 and ileal gene expression of TNF-α, were observed. Moreover, increased relative composition of bacterial communities of genus *Prevotella* and *Anaerovibrio* and decreased populations of the *Clostridium* and *Terrisporobacter* genera were reported for the GLU-supplemented groups. Additionally, findings from the study of Koo et al. (2020) demonstrated an increased villus height and goblet cell density, along with increased expression of jejunal occludens and downregulation of IL-6 in pigs fed 115% standardized ileal digestible (SID) requirements of *L*-threonine.

5 Phenolic Antioxidants

Several agricultural by-products could be suggested as excellent sources of phenolic and antioxidant compounds that can be administered as functional ingredients in livestock feeding (Castrica et al. 2019). Up today, about 8000 phenolic compound structures have been identified (Vuolo et al. 2019), whereas the most widely tested are phenolic acid, flavonoids, tannins, avenanthramides, alkylresorcinols, oligomeric proanthocyanidins, and lignans (Dykes and Rooney 2007; Christaki et al. 2020) originating from plant tissues like grains, vegetables, fruits, trees, and their extract (Dykes and Rooney 2007; Jamwal et al. 2018; Rosa et al. 2019). Natural phenolic antioxidants include the following (Shahidi and Ambigaipalan 2015):

I. Phenolic acids (e.g., benzoic acid, ferulic acid, gallic acid, vanillin)
II. Flavonoids (flavonols, flavononols, flavones, flavanones, anthocyanidins, isoflavonoids)
III. Stilbenes (resveratrol)
IV. Coumarins
V. Lignans
VI. Tannins

Phenols have naturally antioxidant properties; thus, they are capable of protecting biomolecules (proteins, nucleic acids, polyunsaturated lipids, and sugars) from oxidative damage via free radical-mediated reactions (Heleno et al. 2015). Reactive oxygen radicals could disrupt nutrient absorption after affecting the intestinal mucosa, whereas antioxidants can neutralize reactive oxygen radicals and improve intestinal function (Valenzuela-Grijalva et al. 2017). The increase of reactive oxygen species (ROS) around weaning and disturbance of cellular antioxidant systems balance, as demonstrated by reduced superoxide dismutase (SOD) and glutathione peroxidase (GPX), are related to disruption of intestinal function (Humphrey et al. 2019). Substances with antioxidant properties could enhance immunocompetence or through their co-enzymatic activity could affect cell-to-cell communication, thereby modulating immune system reactions (Catoni et al. 2008).

Polyphenols and, in some cases, flavonoids have been shown to reduce the effect of the above-mentioned phenomena supporting immune and inflammatory cell functions (Shi et al. 2003; Xu et al. 2014). Carotenoids, vitamin C, and vitamin E have been also suggested as substances that can improve both specific and non-specific immune responses in several species (Catoni et al. 2008). Furthermore, in a study with piglets, dietary supplementation of a polyphenol mixture (from apples, grape seeds, green tea leaves, and olive leaves) resulted in reduced plasma malondialdehyde (Zhang et al. 2014), whereas supplementation of grape seed procyanidins as phenolic compounds increased resistance to weaning stress through the enhancement of glutathione peroxidase (GSH-Px), SOD, and catalase (CAT) genes expression (Fang et al. 2020).

Anti-inflammatory properties of phenolic compounds are based on the suppression of inflammatory prostaglandins and nitric oxide production (Valenzuela-Grijalva et al. 2017). Phenolic compounds support, through their mode of action, the production of immunoglobulins and secretion of cytokines, increase of phagocytosis by influencing mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB) signaling pathways (Artuso-Ponte et al. 2020), as well as release of IFN-γ (Christaki et al. 2020). Polyphenol-rich diets in piglets have shown to reduce the expression of different pro-inflammatory genes in duodenum, ileum, and colon (Fiesel et al. 2014), whereas reduced inflammatory mediators NF-κB and Nrf2 (nuclear factor erythroid 2–related factor 2) have been detected in duodenal mucosa of pigs fed with phenol-rich supplemented diets containing grape seed and grape pomace extract (Gessner et al. 2013). Findings from Coddens et al. (2017) on cranberry extracts (rich in proanthocyanin) supported its efficacy on the inhibition of $F4^+$ and $F18^+$ *E. coli* adhesion to the ileum in vitro. Grape by-products have been reported as a beneficial polyphenol source for pigs (Brenes et al. 2016), since the introduction of fermented grape pomace (48.5% dietary inclusion) to 20 days old piglets feed for 30 days (Kafantaris et al. 2018) resulted in the enhancement of the antioxidant defense system along with the increase of *Bifidobacterium* and lactic acid bacteria counts and the reduction of *Enterobacteriaceae* counts. Additionally, tea polyphenols have showed multiple effects on immune response in pigs, since they could influence the activities of T-lymphocyte, increase the ratio of $CD4^+/CD8^+$, and reduce the outcome of oxidative stress. Furthermore, they could improve cell-mediated immune response and the secretion of pro-inflammatory cytokines such as IFN-γ (Deng et al. 2010). They can also improve intestinal mucosal immunity via increasing the content of IL-2, IL-10 in jejunum and ileum and activate the Notch2 signaling pathway in small intestine (Dong et al. 2019).

Antimicrobial and bactericidal properties of phenolic compounds have been also reported. The latter is attributed to their hydroxyl (–OH) groups (Park et al. 2002), whereas antimicrobial effects are based on their structural and lipophilic properties that negatively affect the cellular membrane function of bacteria and can cause cell death (Mahfuz et al. 2021). Findings from trials with supplementation of pig diets with benzoic acid and thyme (Diao et al. 2015), or chestnut wood tannins and organic acids (Brus et al. 2013), or polyphenol-rich grape extract or hop (Fiesel et al. 2014), provided evidence of an improved outcome in terms of reduction of harmful bacteria and improvement of intestinal microbiota.

Significant research findings have been demonstrated from the evaluation of resveratrol (trans-3,5,4′-trihydroxystilbene), which is a stilbenoid, a type of natural polyphenol and aromatic phytoalexin found predominantly in grapes, berries (mulberries), and Japanese knotweed (Ahmed et al. 2013). As reviewed recently by Meng et al. (2023), dietary resveratrol has therapeutic effects on the oxidative stress and inflammation, as well as beneficial effects on growth and meat quality. Significant findings have been described as regards its capability to modulate immune response and inflammation processes. Such effects include stimulation of peripheral blood and splenic lymphocytes proliferation, and improved immune responses to vaccination against classical swine fever and foot-and-mouth disease, whereas it was also found to promote IgG production, regulate the release of IFN-γ, and downregulate the release of TNF-α (Fu et al. 2018). The capability of resveratrol to regulate various signaling pathways such as sirtuin 1, NF-κB, and Nrf enhances the expression of various antioxidant defensive enzymes such as heme oxygenase 1, catalase, GPX, and SOD, and induces glutathione levels responsible for maintaining the cellular redox balance (Truong et al. 2018).

The dietary supplementation of resveratrol alone or with essential oils (oregano, anise, orange peel, and chicory essential oils) in weaned piglets challenged with *E. Coli* and *Salmonella typhimurium* resulted in improved IgG content in the group fed resveratrol only, as well as reduced fecal *Salmonella* and *E. coli* counts in all treatment groups and increased fecal *Lactobacillus* spp. count in the group that received both phytogenic products. The aforementioned results were considered as strong indication of the potential of resveratrol to be used as an antibiotic alternative under the conditions described in that particular study (Ahmed et al. 2013).

Antiviral activity of resveratrol has been reported in various species, whereas its capability to modulate immune response has been reported in rotavirus (RV) and pseudorabies virus (PRV) studies with pigs (Cui et al. 2018; Zhao et al. 2018). A challenge study in piglets suggested that it can be considered as a possible RV infection control measure. It was able to reduce inflammation response by inhibiting the TNF-α production whereas the immune function in RV-infected piglets was maintained by enhancing the IFN-γ content and $CD4^+/CD8^+$ ratio (Cui et al. 2018). Zhao et al. (2018) suggested resveratrol as alternative control measure for PRV infection, since it showed an inhibitory effect on viral reproduction, alleviated PRV-induced inflammation, and enhanced animal immunity (increased the levels of serum TNF-α, IFN-α, IFN-γ, and IL-12). Furthermore, an in vitro study suggested that resveratrol could alleviate *E. coli* K88 infection-induced damage in the porcine intestinal epithelial cell by activating sirtuin 1 signaling pathway (Luo et al. 2022).

6 Eubiotics: Phytobiotics Probiotics, Prebiotics, Postbiotics

According to Wiemann (2013), eubiotics are feed additives that include direct acting gut flora modulators, probiotics, prebiotics, and immune modulators to stimulate a healthy microbiota. Probiotics as beneficial microbes in combination with prebiotics (indigestible dietary fiber/carbohydrate, e.g., inulin) provide health benefits to the animal, through several pathways such as normalization of the microbiota due to probiotics addition, or via products resulting from prebiotics anaerobic fermentation, or through their immunomodulatory role (Hardy et al. 2013). Postbiotics are metabolites and cell contents extracted from probiotics (Teame et al. 2020).

Probiotics, prebiotics, and postbiotics could act as anti-inflammatory factors (Cheng and Kim 2022) since they can stimulate TLR to inhibit NF-κB and activate an anti-inflammatory response (Suda et al. 2014; Poulsen et al. 2018). Selected *Bacillus* species (Taras et al. 2005), as well as *Lactic acid* bacteria (LAB), including *Enterococcus* species (e.g., *Enterococcus faecium*) and *Lactobacillus* species, have shown promising results as functional feed additives for improved immune responses in nursery pigs (Pessione 2012; Suda et al. 2014). Research findings have demonstrated that *Enterococcus faecium* could reduce newborns' mortality and post-weaning diarrhea when fed to sows (Taras et al. 2006) or decrease serum IgG (Broom et al. 2006) and chlamydial infection in newborn piglets from infected sows (Pollmann et al. 2005).

Effects of feeding mannan oligosaccharide (MOS) and *Lactobacillus mucosae* (LM) as prebiotic and probiotic sources in weanling pigs have been previously tested under *Escherichia coli* lipopolysaccharide (LPS) challenge conditions (Li et al. 2021a). Results demonstrated an increase of circulating but not secretory IgG antibodies in MOS-fed groups, as well as a mild increase in both secretory and circulating IgA concentrations in pigs fed LM. In another study by Yu et al. (2021), MOS supplementation in *E. coli*-challenged pigs resulted in reduced IL-1β concentration. Decreased pro-inflammatory cytokines were observed also in pigs fed levan-type fructan (Li and Kim 2013). The prebiotic lactulose has showed immune-boosting effects in pigs (Liu et al. 2018), as it was able to induce greater concentrations of serum IgM and IgA and improved immunity against *Salmonella typhimurium* (Naqid et al. 2015). Moreover, increased cell-mediated immune response, IL-1β gene expression, and serum levels of IL-1β, IL-2, and IL-6 were observed after supplementation of weaned pigs' diets with chitosan and galacto-mannan oligosaccharides (Yin et al. 2008).

Previous studies with *E. coli*-challenged pigs reported increased secretory IgA in animals receiving *Lactobacillus rhamnosus* (Zhang et al. 2010) or *Lactobacillus acidophilus* with increased concentration of IgA in the jejunum (Li et al. 2018). Other studies further supported *Lactobacillus* species' beneficial effects, such as their ability to alleviate gut inflammation, improve intestinal barrier function, and decrease pro-inflammatory cytokines (*L. rhamnosus*) according to Mao et al. (2020) and downregulate IL-1β (*L. fermentum*) based on Wang et al. (2019) findings.

A connection between modulation of sow's intestinal microbiota and suckling piglets' bacterial colonization of the GIT has been reported. Supplementations of probiotics such as *Enterococcus faecium* or *Bacillus subtilis* (Macha et al. 2004; Baker et al. 2013; Starke et al. 2013) and prebiotics such as inulin (Paßlack et al. 2015) in sows diets were able to induce such microbiota alterations. As regards immune response, enrichment of sows' diets with oligosaccharides such as short-chain fructooligosaccharides (scFOS), MOS, or a seaweed extract containing laminarin could be related with an increase of colostral immunity (IgA, IgG, or TGFß) (Czech et al. 2010; Leonard et al. 2012; Le Bourgot et al. 2014).

Beta-glucans, mannoprotein, and chitin are the main cell wall components of yeasts. Beta-glucans derived from yeast cell walls bind to the TLR2 and C-type lectin receptors (CLR) family and dectin-1 receptor on enterocytes and immune cells (monocyte-macrophage cell lineage and other antigen-presenting immunocompetent cells) (Akira et al. 2006; Li et al. 2019a). Through their mode of action, they result in the increase of pro-inflammatory cytokines and chemokines inducing antigen presentation and improvement of humoral and cellular immunity (Vetvicka et al. 2014). Supplementation of sows' gestation and lactation diets with yeasts (e.g., *Saccharomyces cerevisiae* fermentation product) improved growth performance of piglets (Kim et al. 2008, 2010; Shen et al. 2011) and improved beneficial microbiota status in the GIT (Lu et al. 2019).

Moreover, Li et al. (2006) evaluated whether supplementation of pig diet with β-glucan could affect immune response, and presented results of increased plasma IL-6, IL-10, and TNF-α, hours after LPS challenge. Ryan et al. (2012) provided evidence that glucan incorporation in pig feeds results in decreased Th-related cytokine production (reduction of the Th17 signature molecule IL-17a in the porcine colon), whereas increased IgA levels in serum were observed at lower glucan doses provided as yeast (*Saccharomyces cerevisiae*) cell wall extract (Sauerwein et al. 2007). Proportion of $CD4^+$ T-cell subpopulations has been found greater in mesenteric lymph nodes and Peyer's patches, as well as $CD8^+$ T-cells in peripheral blood in pigs fed glucan (Vetvicka et al. 2014). Moreover, stimulation of IL-2 and phagocytosis as well as suppression of TNF-α due to glucan administration in pigs' feed has been reported (Vetvicka and Oliveira 2014).

Fibers include a broad spectrum of oligosaccharides and starch resistant to proximal intestine hydrolysis, as well as non-starch polysaccharides such as pectin, cellulose, hemicellulose, β-glucans, and fructans (Rodrigues et al. 2022). Digestion process of dietary fiber in pigs includes their fermentation primarily in the colon producing gases and several physiologically active by-products. On the other hand, insoluble fiber increases diet bulkiness due to its metabolic inert characteristic (Jarrett and Ashworth 2018). It has been demonstrated that supplementation of a diet with 25% sugar beet pulp in pregnant gilts resulted in increased white blood cells, without affecting natural killer cell cytotoxicity, neutrophil chemotaxis and chemokinesis, mitogen-induced lymphocyte proliferation, and differential counts (McGlone and Fullwood 2001). Moreover, feeding diets rich in crude fibers (different roughage sources, i.e., straw, hay, clover grass silage, maize silage, or Jerusalem artichoke) during pregnancy, but not lactation, resulted in a decrease of C-reactive protein levels in colostrum, suggesting a possible reduction of inflammatory processes (Werner et al. 2014). In growing pigs, it was reported that pigs fed soluble fiber (sugar beet fiber) had reduced fecal egg counts following *Oesophagostomum dentatum* challenge (Petkeviius et al. 2003).

The positive effects of fermentable fibers on immune response and intestinal function are various: the improvement in colonic barrier function and immune/metabolism-related gene expression (Che et al. 2014), the maintenance of microbial community homeostasis, the improvement in microbiota diversity, proliferation of potentially beneficial microorganisms (Li et al. 2020b), as well as the attenuation of the release of inflammatory intermediates (Li et al. 2019b) are among those effects. Moreover, it has been demonstrated that through the promotion of the growth of lactic acid bacteria, the prebiotic inulin has an indirect beneficial immune effect, since it can affect the production of anti-inflammatory cytokines, mononuclear cells, and phagocytic macrophages (Grela et al. 2021). Additionally, it has been associated with the induction of immunoglobulins synthesis, in particular IgA (Macfarlane and Cummings 1999). Thus, it seems that inulin has a positive effect on the intestinal immune system, blood flow through the mucosa, and the activity of the local nervous system (Grela et al. 2021).

7 Phytogenics and Essential Oils

Phytogenics or plant secondary metabolites (Rodrigues et al. 2022) can be classified into:

I. Terpenes (e.g., carvacrol, thymol)
II. Phenolics (e.g., eugenol, resveratrol, quercetin, tannins), which are emphasized for their antioxidant capabilities in a previous part of this chapter
III. N-containing compounds
IV. S-containing compounds (e.g., alliin and allicin)

Novel technologies allow us to chemically synthesize some of the above-mentioned substances and these products can be called nature-identical compounds (Rossi et al. 2020). Such compounds (e.g., thymol and vanillin) can act synergically in combination with other feed additives in pigs' diets (Rodrigues et al. 2022). Essential oils are either terpenes or phenolics and are usually extracted from plants, whereas their antimicrobial, anti-inflammatory, and antioxidative properties are attributed mainly to their phenolic ring, or capacity to disturb microbial membranes and intracellular homeostasis (Omonijo et al. 2018).

Plants from the *Echinacea* family are known to modulate immune functions, stimulating the innate immune system, and increasing the resistance to infection (Bauer et al. 1999), whereas improved immune response after vaccination against *Erysipelothrix rhusiopathiae* was observed after inclusion of *Echinacea purpurea* into the diet of finishers (Maass et al. 2005). On the other hand, Taranu et al. (2012) provided further evidence that introduction of *Chlorella vulgaris* powder (eukaryotic freshwater green microalga), Na-alginate, inulin, and a mixture of essential oils into diets of weaned piglets resulted in increased IgG in the plasma, modulation of cytokine production, and mineral retention (increased liver concentrations of IL-1β, IL-8, TNF-α, IFN-γ, Cu, and Fe). A possible interaction of active molecules from the test products (polyphenols, vitamins, minerals, etc.) as additional ligands with Fc-gamma receptors for IgG (FcgammaRs) and their further influence on the immune system could be supported as an explanation for the observed increased IgG levels (Nimmerjahn and Ravetch 2010).

Plant extracts like cinnamon, thyme, oregano (Namkung et al. 2004), and saponin (Ilsley et al. 2005) were able to increase IgG concentration in pigs. On the other hand, studies from Ilsley et al. (2005) and Ariza-Nieto et al. (2011) suggested absence of IgG levels increase after dietary curcumin or oregano essential oil supplementation. As regards modes of action of the plant extracts on cellular immunity and cytokine production, a possible potentiation of the immune reaction through the increase of IFN-γ production, and the involvement of a Th1 rather than Th2 type of cellular immunity, as well as their anti-inflammatory properties (activation of the NF-κB pathway), have been reported (Taranu et al. 2012). Novel herbal feed additives (Guizhi Li-Zhong Tang extract granules) have been tested with encouraging results on alleviating or preventing pneumonia in weaned piglets, through the inhibition of angiotensin-converting enzyme 2 expression along with increased IgA and IgG, but reduced IgE levels (Lu et al. 2021). A greater antioxidant capacity and lower cytotoxicity of those herbal feed additives was based on findings of enhanced expression of antioxidant-related SOD2 and lower expression of oxidative-stress-related 3-nitrotyrosine (NT), inflammation-related TNF-α and NF-κB, and apoptosis-related caspase-3 in lung tissue (Wang et al. 2021).

Thymol and carvacrol, active components of plant essential oils, can increase the percentage of $CD4^+$, $CD8^+$, major histocompatibility complex (MHC class II, and non-T/non-B-cells in peripheral blood, and $CD4^+$, $CD8^+$ double-positive T-lymphocytes in peripheral blood and mesenteric lymph nodes in pigs (Walter and Bilkei 2004). Moreover, thymol enhances total IgA and IgM serum levels, and exhibits particular local anti-inflammatory properties, as demonstrated with the reduction of TNF-α mRNA in the stomach of post-weaned pigs (Trevisi et al. 2007). Additional evidence provided by Li et al. (2012) after the introduction of an essential oil product, which contained 18% thymol and cinnamaldehyde in weaned pigs' diets, suggested immune-modulating beneficial properties that could position such products as antibiotic replacements in pigs' diets. Results included reduced IL-6 concentration and increased TNF-α and total antioxidant capacity levels in plasma, as well as greater villus height to crypt depth ratio and reduced *E. coli* populations in cecum, colon, and rectum. Quite similarly, Nofrarías et al. (2006) supported the capability of essential oils to induce an improved immune response, as demonstrated in immune cell subsets of gut tissues and blood after the introduction of a plant extracts mixture with 5% carvacrol, 3% cinnamaldehyde, and 2% capsicum oleoresin (CAP) in weaned pigs' diets. Essential oil compounds from oregano, clove, and cinnamon were also tested by Halas et al. (2011) and results suggested enhancement of the non-specific immunocompetence of 28-days-old pigs.

As regards viral challenges, capsicum oleoresin (CAP), garlic botanical (GAR), or turmeric oleoresin (TUR) were tested in vivo under porcine reproductive and respiratory syndrome virus (PRRSV) challenge conditions (Liu et al. 2013). Findings suggested various effects on the immune response of animals fed the plant extracts. Feeding GAR increased B-cells and $CD8^+$ T-cells of PRRSV-infected pigs, suggesting an improvement of immune response. Anti-inflammatory effects of the extracts were suggested due to suppressed serum TNF-α and IL-1β production in PRRSV-challenged animals that received the test products. Quite similarly, Kim et al. (2020) provided evidence that the aforementioned substances (i.e., CAP, GAR, TUR) altered the expression of 46 genes (24 up, 22 down), 134 genes (59 up, 75 down), or 98 genes (55 up, 43 down) in alveolar macrophages of PRRSV-infected pigs. Supplementation of diets with TUR or GAR reduced the expression of genes associated with antigen processing and presentation, whereas introduction of CAP upregulated the expression of genes involved in those processes.

As reviewed by Li et al. (2021b), sugar cane extracts can enhance immune response in PRV-challenged pigs, through the increase of natural killer cytotoxicity, lymphocyte proliferation, phagocytosis by monocytes, and IFN-γ production of $CD4^+$ and γδ T-cells (Lo et al. 2006). Studies on porcine epidemic diarrhea virus (PEDV) suggested isoflavonoid (major component of puerarin from the Chinese herb Gegen) could regulate the interferon and NF-κB signaling pathways and provide antiviral and anti-inflammatory functions in PEDV-infected piglets (Wu et al. 2020), whereas tomatidine can inhibit the virus replication mainly by targeting 3-chymotrypsin-like (3CL) protease (Wang et al. 2020). Recent data on the devastating African swine fever virus (ASFV) suggested that the introduction of a formulation with three essential oils, i.e., *Eucalyptus globulus*, *Pinus sylvestris*, and *Lavandula latifolia*, can improve immune response resulting in enhanced IgG levels and reduced IgM levels and minimize ASFV transmission in pigs in vivo (Babikian et al. 2021).

Taken together, immune-boosting functions of phytogenic products could include the modulation of leukocyte and neutrophil activation processes of the innate immune system (Firmino et al. 2021). They improve the activity of various immune cells such as lymphocytes, macrophages, and NK cells, thus enhancing phagocytosis and IFN synthesis (Kuralkar and Kuralkar 2021). The enhancement of the immune activities of polymorphonuclear leucocytes (PMNs), alteration of the lymphocyte proportion and the ratio of $CD4^+$ and $CD8^+$ T-cells, downregulation of NF-κB (and p38 pathway) on peripheral blood mononuclear cells (PBMCs), which is responsible for gene transcription, thus of encoding many pro-inflammatory cytokines and chemokines, are among the major immune-modulating actions provoked by phytogenics (Oeckinghaus et al. 2011; Huang et al. 2012; Stelter et al. 2013; Cappelli et al. 2021). Furthermore, alterations on blood percentages of Th lymphocytes, γδ T-lymphocytes, and B-lymphocytes could be observed (Lo Verso et al. 2020). Depending on each essential oil mode of action, they could increase serum concentrations of IL-1, IL-2, IL-4, IL-6, TNF-α, soluble surface antigen CD8 (sCD8), immunoglobulins IgA, IgG, and IgM, the activities of antioxidant enzymes, and total antioxidative capacity, and decrease concentrations of malondialdehyde (e.g., water extract of *Artemisia ordosica*) (Xing et al. 2019). Other cases (e.g., anethole) could result in reduced expression of TLR5, TLR9, MyD88, IL-1β, TNF-α, IL-6, and IL-10 in the jejunum (Yi et al. 2021). Additional anti-inflammatory properties have been attributed to the inhibition of the NF-κB and P38 signaling pathways, which result in decrease of inflammatory cytokine expression (e.g., *Scutellaria baicalensis* extracts) (Huang et al. 2019). In addition to the NF-κB pathway, the antioxidative, anti-apoptotic, and anti-inflammatory effects of essential oils (e.g., *Tagetes erecta* flowers essential oils) may rely on Nrf2/HO-1 since Nrf2 has a significant role in protection of cells against oxidative damage as well as in cell survival (Shaw and Chattopadhyay 2020). The increased expression of antioxidant-related genes could also explain the antioxidant capabilities of essential oils as observed for cinnamaldehyde and thymol in pigs (Su et al. 2018).

8 Organic Acids (OAs)

Classification of OAs includes three categories based on the carbon chain:

I. Short-chain fatty acids (SCFAs; e.g., formic acid, acetic acid, propionic acid, butyric acid)
II. Medium-chain fatty acids (MCFAs; e.g., caproic acid, caprylic acid, capric acid, lauric acid)
III. Tricarboxylic acids (e.g., citric acid, fumaric acid, and malic acid) (Rodrigues et al. 2022)

OAs possess bacteriostatic and bactericidal actions, since they can diffuse across the bacterial cell membranes, release H^+ ions intracellularly, and disrupt the acid–base balance and particular metabolic pathways of microbes (Nguyen et al. 2020).

A combination of OA utilization may be significantly beneficial for pigs, since SCFAs have been proven efficacious against Gram (−) bacteria, including *E. coli* and *Salmonella* spp., whereas MCFAs were efficacious against Gram (+) bacteria, such as *C. perfringens* and *Streptococcus* spp. (Zentek et al. 2011; Gómez-García et al. 2019). Furthermore, particular immunomodulatory effects of OAs have been demonstrated in enterotoxic *Escherichia coli* (ETEC)-challenged pigs. Among those, decreased concentration of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and IFN-γ in plasma) was observed at levels comparable to antibiotics supplementation (Ren et al. 2019). According to Jiménez et al. (2020), feed supplementation with an organic acid-based feed additive reduced the number of inflammatory cells in the jejunal and ileal lamina propria, which were elevated due to inoculation with an enterotoxic strain of E. coli (K88) in weaned pigs. Moreover, it has been demonstrated that conjugated linoleic acid fed in late gestation and (or) lactation to sows could induce positive immunomodulatory effects on colostrum, milk, and progeny serum IgG concentrations (Craig et al. 2019).

Immunomodulatory properties have been also reported for certain MCFAs and monoglycerides, such as the C12 monoglyceride (glycerol monolaurate, GML), which is known to affect T-cell lymphocytes, due to membrane interactions linked to cell signaling pathways (Jackman et al. 2020; Zhang et al. 2018). GML supplementation can also decrease cytokine production in vitro, thus inducing immunosuppressive effects that can be useful for anti-inflammatory applications (Zhang et al. 2016). Oral administration of GML could reduce intestinal inflammation in vivo (Zhang et al. 2018). Findings from an in vitro study demonstrated that caprylic (C8), capric (C10), and lauric (C12) acids could enhance immune response at a porcine intestinal cell line (Martínez-Vallespín et al. 2016).

9 Concluding Remarks

A significant number of feed additives that could improve the immune response of pigs and act as anti-inflammatory and antioxidant agents have been investigated and the list will continue to expand as novel research findings are presented. As observed from the above-mentioned studies, a combination of the beneficial feed additives is expected to result in improvement of the pig's response against pathogens and provide solutions as alternative to antibiotics substances. However, the addition of the additives should take into account the observed health challenges at the farm, as well as restrictions on the use of particular feed additives either alone or in combination with others. It is possible that the target of eubiosis and improved health status of pigs could be achieved or assisted through appropriate feed interventions with the administration of more "natural" substances, which enhance immune response in pigs.

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