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Feed additives of bacterial origin as an immunoprotective or imunostimulating factor

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Feed additives of bacterial origin as an immunoprotective or imunostimulating factor

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Abstract

Since January 2006 when using antibiotics as growth promoters in animal feed have been banned scientists are looking for the best resolution to apply alternative substances. Extensive research into the health-promoting properties of probiotics and prebiotics has led to significant interest in the mechanisms of action of the combined administration of these feed additives as a synbiotic. Subsequent research has led to the development of new products. Among the most important health benefits of additives are, inhibiting the growth of pathogenic bacteria in the GI tract, maintenance of homeostasis, treatment of inflammatory bowel diseases, and increase in immunity. Specific immunomodulatory mechanisms of action are not well understood and the effect is not always positive, though there are no reports of adverse effects of these substances found in the literature. For this reason, research is still being conducted on their proper application. However, due to the difficulties of carrying out research on humans, evidence of the beneficial effect of these additives comes mainly from experiments on animals. The objective of the present work was to

assess the effect of probiotics, prebiotics, and synbiotics, as well as new additives including postbiotics, proteobiotics, nutribiotics, and pharmabiotics, on specific immunomodulatory mechanisms of action, increase in immunity, the reduction of a broad spectrum of diseases.
Key words: probiotic, prebiotic, synbiotic, postbiotic, proteobiotic, nutribiotics, pharmabiotics

Since the ban on antibiotic growth stimulators was introduced in 2006 there has been increasing pressure to reduce the use of pharmacological doses of some preparations and chemotherapeutics in animal production (Schwarz et al., 2001; Lynegaard et al., 2021; Sazykin et al., 2021). Fortunately, feed additives look to be promising candidates to replace such banned substances. According to the European Commission, feed additives are products used in animal nutrition that improve the quality of feed and food of animal origin and / or improve the efficiency and health of the animals fed with them. In practice, a whole range of various types of feed additives are used, and each of them has a specific spectrum of activity (Jacela et al., 2009). According to article 6 (Regulation (EC) No 1831/2003), feed additives are divided into 5 groups: 1) technological: any substance added to feed for a technological purpose; 2) sensory: any substance that improves or changes the organoleptic properties of the feed, or the visual characteristics of the food derived from animals; 3) nutritional: the addition of which improves or maintains the nutritive value of the feed; 4) zootechnical: any additive used to favorably affect the performance of animals in good health or used to favorably affect the environment; 5) coccidiostats and histomonostats: substances intended to inhibit or destroy protozoa that cause coccidiosis or histomoniasis. Sometimes this division is not sufficient to accurately describe the properties of a particular product, and in these instances the term "functional additives" is used to more clearly define their purpose (Pluske, 2013; Gainullina et al., 2020; Verso et al., 2020). In general, feed additives, due to their pro-health effects, can be divided into two basic groups: immunoprotective and immunostimulating (Szuba-Trznadel et al., 2014; Satora et al., 2021).

Immunoprotection is primarily based on a direct fight against pathogens, and should be effective enough to induce a targeted immune response of the host to antigen (Marshall et al., 2018; Mondal and Thomas, 2022). For example, such an effect can be achieved through inducing optimal pH or balancing the amount of beneficial and pathogenic microflora in the intestine. It could be obtained by supplementation of *Bacillus* sp. to pigs' diet. This probiotic bacteria reduce pH in intestines what favors *Lactobacilli* and inhibits *E.coli* and *Salmonella* (Celi et al., 2017; Nguyen et al., 2019; Kim et al., 2019). Immunostimulation relies on activation of cells of the host immune system such as macrophages, natural killer cells, dendritic cells, and T and B lymphocytes, that produce humoral elements including cytokines, acute phase proteins, and immunoglobulins (Böhmer et al., 2009; El-Rahim, 2017). Wang et al. (2016) reported beneficial immunomodulatory properties of probiotic bacteria which prevented increasing of proinflamantory citokines Il-6 and TNF-α caused by ETEC and slightly induced anti-inflamantory IL-10. Roselli et al. (2007) reported similar observations. These mechanisms can be induced in animals by the addition of live bacteria, or compounds produced by bacteria, that stimulate the growth or activity of the desired microorganisms (Celi et al., 2017; El-Rahim, 2017). This group of additives is represented by probiotics, prebiotics, synbiotics, proteobiotics, and postbiotics (Pan et al., 2017; Verso et al., 2020; Kiarie et al., 2022). In order to achieve the desired effect of these additives they have to be resistant to feed production and storage conditions, as well as the environment of the host's digestive system (Bourebaba et al., 2022).

The objective of the present work was to present a brief overview of known feed additives like: pro-, pre- and synbiotics and enrich it with new products belonging to this group which appeared in last years: postbiotics, proteobiotics, nutribiotics, and pharmabiotics.

Characteristics of feed additives

Probiotics

The definition of a probiotic was formulated in 2002 by experts from the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). Probiotics are characterized as "live strains of well-defined microorganisms which, when administered in adequate amounts, ensure an appropriate bacterial balance of the intestinal flora and have a beneficial effect on the health of the consumer" (FAO, 2002). This definition was maintained in 2013 by the International Scientific Association for Probiotics and Prebiotics (ISAPP). Their primary role, thanks to their ability to rapidly multiply, is to colonize the intestine and stabilize the intestinal microflora (Ricke and Pillai, 1999; Bernardeau et al., 2006; Liao and Nyachoti, 2017). They reduce the pathogenicity of harmful bacteria by competing with them for resources such as nutrients or a place to live and we can expect intestinal eubiosis as well as more efficient host immune response (Nisbet, 2002; Dong et al., 2014; Liao and Nyachoti, 2017; Roselli et al., 2017). It is widely reported and confirmed that this additive improve growth performance (Suo et al., 2012; Yang et al., 2020; Wang et al., 2021 a). They help to maintain optimal acidity of the gastrointestinal (GI) tract through the production of organic acids, as well as supporting the digestion of food through the production of enzymes what can decrease diarrhoea incidents, especially in young pigs (D'Inca, 2011; Rowland et al., 2018; Yadav and Jha, 2019; Tugnoli et al., 2020). In the addition they can reduce faecal noxious gas emission what can decrease environmental pollutions (Zhao and Kim, 2015; Liu et al., 2018; Nguyen et al., 2019).

The most common microorganisms with probiotic activity in animals are non-spore forming bacteria belonging to the genera *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus,* and *Pediococcus*. Additionally, there are spore forming *Bacillus and Clostridium* species, as well as probiotic yeasts of the genera *Saccharomyces* and *Kluyveromyces* (EFSA, 2013). Probiotics can be used as a single strain additive or as multi-strain mixtures, with the latter formulations producing greater efficiency through higher fattening, slaughtering performance, and better overall health (Kwak et al., 2021). Despite the commonly known beneficial properties of probiotics on the health status of the host, we must also mention the little-known / explained their detrimental properties (Lambo et al., 2021; Wang et al., 2021 b). Nataraj et al. (2020) points some limitations for using probiotics like: unknown molecular mechanisms as well as changeable properties during technology process, developing antibiotic resistance, bacterial translocation to tissue or blood, unknown the right dose of this additive in different conditions of animals maintenance.

Prebiotics

In 2007, FAO/WHO experts defined prebiotics as non-viable nutrients that exert beneficial effects on host health due to modulation of the gut microbial community (FAO, 2007). Prebiotics are not digested, or only partially digested, which allows them to reach the large intestine where they are fermented and selectively stimulate the growth and/or activity of a limited number of bacteria in the colon (Macfarlane et al., 2008; Shigwedha et al., 2016; Davani-Davari, 2019). This fermentation can lead to an increase in short-chain fatty acids (SCFAs), an increase in fecal mass, a moderate reduction in colonic pH, and a reduction in nitrogenous end products (predominately ammonia, urea and uric acid) and fecal enzymes (Crittenden and Playne, 2009; Azad et al., 2020; Markowiak-Kopeć and Śliżewska, 2020). Moreover they are involved in the modulation of lipid metabolism, increased calcium absorption, confer beneficial effects on the immune system, and modify intestinal function (Brestenský et al., 2016 a, b; Whisner and Castillo, 2018; Al-Shawi et al., 2020; Azad et al., 2020; Niu et al., 2022). Additionally, SCFAs from the fermentation process such as acetic acid, butyric acid, and propionic acid, may be used by the host as an energy source (Yoo and Kim, 2016; Shimizu et al., 2019; Żółkiewicz et al., 2020; He et al., 2020). This action also stimulates the growth and / or activity and survival of beneficial intestinal bacteria, mainly of the genera *Bifidobacterium* and *Lactobacillus* (Roberfroid, 2007; Liu et al., 2015; Markowiak and Śliżewska, 2018; Davani-Davari et al., 2019; Shehata et al., 2022; Wang et al., 2020). These bacteria constitute a selective group of beneficial species of microorganisms that contribute to the prevention of pathogenic bacteria colonization by competing for cellular receptors and nutrients (Netherwood et al., 1999; Higgins et al., 2010; Monteagudo-Mera et al., 2019; Shehata et al., 2022).

Prebiotics found in human or animal nutrition are a very large group of substances with varying mechanisms of action, and include fructooligosaccharides, galactooligosaccharides, isomaltooligosaccharides, xylooligosaccharides, soybean oligosaccharides, mannanoligosaccharides, lactuloses and lactosucrose. This is in addition to substances such as fiber and its degradation products, including pectins, xylans, and celluloses (Czech et al., 2006; Fritz, 2007; Gibson et al., 2017).

Prebiotics can stimulate or modulate the immune system of the host by altering mucus production, inhibiting attachment to enterocytes by harmful bacteria, increasing cell stabilization, and stimulation of secretory IgA production (Markowiak and Śliżewska, 2018; Teng and Kim, 2018; Azad et al., 2020; Pujari and Banerjee, 2021).

Synbiotics

Synbiotics are defined as the combination of probiotics and prebiotics into one product. According to the ISAPP, synbiotics are a mixture of live microorganisms and substrate(s) selectively utilized by host microorganisms to confer a health benefit on the host (Swanson et al., 2020). Such mixtures consist of “good” bacteria (probiotics) and a nondigestible carbohydrate source (prebiotics) that encourage the growth of beneficial bacteria by favorably modifying the intestinal microflora and metabolism (Awad et al., 2009; El-Banna et al., 2010; Koyun et al., 2022; Melara et al., 2022). Benefits of regular consumption of probiotics and prebiotics include enhanced immune function, improved colonic integrity, decreased incidence and duration of intestinal infections, downregulated allergic responses, and improved digestion (Muzaffar et al., 2021). It is assumed that the individual properties of pre- and probiotics may complement each other or act synergistically (Markowiak and Śliżewska, 2018; Muzaffar et al., 2021; Reehana et al., 2021).Studies have suggested that prebiotics may increase the survival of probiotic bacteria that pass through the upper GI tract and thus enhance their activity in the large intestine (Fooks et al., 1999; Roberfroid, 2000; Yan and Polk, 2020; Da Silva et al., 2021). It is also understood that the individual properties of pre- and probiotics may be complementary or they may act synergistically (Bielecka et al., 2002; Muzaffar et al., 2021; Reehana et al., 2021). Complementary synbiotics are comprised of a probiotic and a prebiotic that work independently to achieve one or more health benefits. On the other hand, synergistic synbiotics are composed of a live microorganism and a selective substrate that enhances the health benefit delivered by the co-administered live microorganism (Swanson et al., 2020). While the benefits of probiotics and prebiotics are known, scientists are cautious about drawing firm conclusions. Observed benefits depend on the type and amount as well as the ratio between pro- and prebiotics, which are difficult to predict (Reehana et al., 2021).

Postbiotics

The term postbiotic is relatively new in the literature, appearing in the last 10 years, and there are many definitions. In 2021 ISAPP proposed a new definition: a postbiotic is a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host (Salminen et al., 2021). In practice, the term was introduced to distinguish live bacterial cells (probiotics) from a bioactive product containing dead microorganisms and their metabolites, such as soluble factors secreted by live bacteria or released after bacterial lysis of probiotic strains. This includes enzymes, peptides, teichoic acids, cell surface proteins, polysaccharides and organic acids (Aguilar-Toaláa et al., 2018). According to Salminen et al. (2021) there are a number of different terms for this additive in the literature, including paraprobiotics, parapsychobiotics, ghost probiotics, metabiotics, tyndallized probiotics, and bacterial lysate, all of which are described as different products. Worth mentioning is the distinction in this group done by Nataraj et al. (2020), where: postbiotics may be defined as "non-viable bacterial products or metabolic products from microorganisms that have biological activity in the host paraprobiotics (also called ghost or inactivated probiotics) that are "non-viable microbial cells (either intact or broken) or crude cell extracts which when administered (either orally or topically) in adequate amounts, confer a benefit on the human or animal consumer"; and probioceuticals / probiotaceuticals which defines probiotic derived factors such as reuterin from *Lactobacillus reuteri*. This indicates the importance of standardizing commonly used terms.

Fermentation is the process that triggers the formation of postbiotics. After fermentation numerous non-viable cells (postbiotics) are slightly acidic what suppress the growth of pathogens and thanks to it they are more stable during prolonged storage, thermal treatments or processes (Pelton, 2020; Salminen et al., 2021; Pérez-Alvarado et al., 2022). In the vast majority of cases, postbiotics are identified as metabolites of probiotic strains such as, *Bifidobacterium breve, B. lactis, B. infantis, Bacteroides fragilis,* and *Lactobacillus* (Tomasik and Tomasik, 2020). Therefore, dead cells can trigger a biological response as effectively as their live equivalents. Administration of postbiotics in adequate amounts confers benefit to the human or animal consumer, and they are better than probiotics in some clinical cases (Siciliano et al., 2021). Their advantages include eliminating the risk of bacterial translocation, transferring antibiotic resistance genes, and being easier to produce, transport, and store are in favor of their use (Puccetti et al., 2020; Martyniak et al., 2021; Siciliano et al., 2021). Furthermore, due to the absence of bacterial multiplication, they are administered in strictly adequate amounts, so that their therapeutic effects are more precise and reproducible.

The action of postbiotics is multidirectional, but the most important is their immunomodulatory properties. For instance, proteins and peptidoglycans of lactic acid bacteria and lipoteichoic acid from Gram-positive bacteria can stimulate the immune system or inhibit the excessive response of monocytes.

In addition, some postbiotic proteins can improve digestion by helping to regenerate the mucosa and intestinal walls (Martyniak et al., 2021).

Proteobiotics, nutribiotics and pharmabiotics

Novel terms are emerging in human medicine that do not yet have well-established definitions. Proteobiotics have been described as metabolites from probiotics (Tarsillo and Priefer, 2020). In contrast to postbiotics, they don't contain microbial cells but it still is difficult to differentiate between them. Nutribiotics are probiotics that confer nutritional benefits by producing essential nutrients, such as vitamins and minerals, and by converting precursors to bioactive metabolites (Chaudhari and Dwivedi, 2022). Pharmabiotics are probiotic products with a proven pharmacological action in health or disease (Chaudhari and Dwivedi, 2022).

Table 1 presents examples of the most commonly used commercial feed additives from the group described above: "-biotics".

Table 1. Functional feed additives consisted of life bacteria, their metabolites or inactivated cell, as well as compounds influencing their growth or metabolic activity (Hamasalim, 2016; Kiczorowska et al., 2017; Novik and Savich, 2020; Tarsillo and Priefer, 2020; Sella et al., 2021; Siciliano et al., 2021; Canibe et al., 2022; Chaudhari and Dwivedi, 2022)

Feed additive	Examples
Probiotic	*Bacillus* sps. *(B. coagulans*, *B. licheniformis*, *B. subtilis B. subtilis natto)*, *Bifidobacterium* sps. *(B. animalis*, *B. bifidum*, *B. longum)*, *Bulgaricus*, *Carnobacterium divergens*, *Enterococcus faecium*, *Lactobacillus* sps. *(L. acidophilus*, *L. amylovorus*, *L. brevis*, *L. casei*, *L. dalbrueckii subsp. L. fermentum*, *L. lactis*, *L. plantarum*, *L. rhamnosus*, *L. salivarius)*, *Pediococcus faecium*, *Saccharomyces* sps., *Streptococcus* sps., *Propionibacterium*, *Clostridium butyricum*, *Pediococcus*, *Lactococcus*, *Leuconostoc*, *Kluyveromyces*
Prebiotic	Inulin, Fructooligosaccharides (FOS), Galaktooligosaccharides (GOS), Lactulose, Lactitol,

	Cereal fibers, Xylooligosaccharides, yest cell wall products
Synbiotic	*Lactobacilli* + inulin, *Bifidobacteria* + FOS, *Lactobacillus* sp. + FOS, *Bifidobacteria i Lactobacilli* + inulin, *Bifidobacteria i Lactobacilli* + FOS, *Lactobacilli* + lactitol, *Bifidobacteria* + GOS, life yest and yest cell wall
Postbiotic	short-chain fatty acids, secreted biosurfactants, secreted proteins, organic acids, amino acids, bacteriocins, vitamins, peptides, peptidoglycan-derived muropeptides, cell surface-associated proteins, cell wall-bound biosurfactants, lipopolysaccharides, exopolysaccharides, lipoteichoic acids, mannoprotein, teichoic acids, fimbriae, chitin
Proteobiotic	metabolites produced by the six strains of *Lactobacillus plantarum*
Nutribiotics	probiotics that confer nutritional functions by producing essential nutrients, such as vitamins and minerals, and converting precursors to bioactive metabolites.
Pharmabiotics	probiotic products with a proven pharmacological action in health or disease

Health-promoting properties

The GI tract is colonized by a vast array of microbial populations that changes in response to changes in the environment, and play a significant role in the health of the host.

Intestinal microflora are an important source of energy during the development and maturation of the intestine, with SCFA produced by bacteria in the large intestine stimulating endothelial cell proliferation. This is optimally achieved through the production of butyric acid (C4), which is a source of energy and a stimulator of growth and differentiation for colonocytes, and propionic acid (C3), which is a substrate of many metabolic processes (Liong and Shah, 2005; Roberfroid, 2007; Gibson and Roberfroid, 2008).

Disturbances to microbiological balance contributes to the development of diseases of the digestive system such as allergies, inflammation, and cancers, as well as improper intestinal peristalsis that can lead to constipation, or diarrhea. Distorted intestinal physiology has a negative impact on the composition of the normal flora and the microbiological barrier in the mucosal lymphoid tissue of the small intestine. This indirectly affects the whole immune system and the proper absorption of nutrients essential for optimal growth (Gibson and Roberfroid, 2008; Górska et al., 2009; Siwek et al., 2018; Andersen et al., 2019).

It has been observed in animals that antibiotic treatment can result in a decreased population of beneficial bacteria, including *Lactobacilli* and *Bifidobacteria* species, along with an increase in the population of potentially pathogenic bacteria. Probiotics can be used to remedy this through promoting the regeneration of the normal flora after antibiotic therapy, which could be further enhanced by administering them immediately after birth / *in ovo*, or during first days of life. This is a common practice in the piglets and chicks industry (Wang et al., 2019; Alizadeh et al., 2022).

Some probiotics, such as the yeast, *Saccharomyces boulardii,* are naturally resistant to antibiotics. This means they can be used as an active means of the inhibition and treatment of diarrhea induced by an imbalance of the intestinal microbiota. Furthermore, *S. boulardii* also binds to pathogenic enteric bacteria and neutralizes their toxins (Stier and Bischoff, 2017; Ansari et al., 2021).

Numerous reports have also highlighted the use of synbiotics in human cancer treatment (Rafter et al., 2007; Fotiadis et al., 2008; Mego et al., 2013; Scott et al., 2018; Alam et al., 2022; Fuad et al., 2022), with studies conducted by Gibson and Roberfroid (2008), Beski and Al-Sardary (2015), Kvakova et al. (2021) indicating that synbiotics better protected consumers from carcinogenic compounds when compared to probiotics and prebiotics used separately.

Maintenance of the intestinal microflora and environment

Host intestinal microbiome composition is shaped by multiple factors such as genetics, diet, and environment. It is believed that during fetal life the GI tract is sterile and its colonization begins immediately after birth, predominantly by bacteria of maternal origin such as *Escherichia coli*, *Lactobacillus,* and *Bifidobacterium*. Other research has shown that microbes are also vertically transmitted to infants from their mothers, as demonstrated by the microbial composition of the meconium from babies born by caesarean section (Blaser, 2006; Moles et al., 2013; Ardissone et al., 2014; Anwar et al., 2019).

Moreover, the presence of microbes in the umbilical cord blood of preterm babies and in the amniotic fluid substantiate indicates that the womb is not completely sterile (DiGiulio et al., 2008; Moeller et al., 2018; Anwar et al., 2019).

Composition of the normal flora is not constant and undergoes gradual changes through effects of the environment and diet (Anwar et al., 2019). Probiotics compete with pathogens for essential nutrients and increase the secretion of mucins, glycoproteins that seal the intestinal epithelium, and change the structure of bacterial toxin receptors. Lactose fermenting bacteria are the main source of polyamines, such as putrescine, spermine, and spermidine, which play an important role in the growth and differentiation of cells. These polyamines reduce the permeability of the intestinal mucosa and stimulates its regeneration. Pro- and prebiotics may also produce substances that inhibit pathogens and promote restructuring of the microflora of the GI tract (Muhammad et al., 2016; Jha et al., 2020; Shehata et al., 2022). Through this competitive exclusion of harmful bacteria the desired balance of intestinal microflora can be achieved, which improves the digestion of feeds and increases feed conversion ratio while lowering production costs (San Andres et al., 2019).

The influence of probiotics on the composition of intestinal normal flora is largely related to their metabolism, particularly the process of carbohydrate fermentation. This produces gases and organic compounds such as lactic acid and SCFAs that lower the pH of the intestine. Lowering the pH of the intestine and the production of substances by probiotics, such as bacteriocins and hydrogen peroxide, has bacteriostatic effects and favors the maintenance of beneficial colonic microflora. There is a body of work suggesting that the fermentation process in the large intestine can be controlled in order to regulate the SCFA composition and content, which is achieved by selecting appropriate probiotics and prebiotics in feed preparations offered to animals (Ziemer and Gibson, 1998; Yadav et al., 2016; Akhtar et al., 2022; Islam et al., 2022). In turn, this inhibits the activity of some bacterial enzymes and pathogenic bacteria (Roberfroid, 2000; Saulnier et al., 2009; Mizak et al., 2012). Furthermore, low pH increases the solubility of calcium and magnesium salts and increases the absorption of calcium and magnesium ions, leading to increased bone density (Heuvel and Weidauer, 1999, Mizak et al., 2012).

Some research has suggested that synbiotics improve the absorption of minerals such as calcium, magnesium, and iron, as well as the synthesis of various B vitamins, which are necessary for proper functioning and growth of animals (Butler et al., 2007; Lopez et al., 2007; Beski and Al–Sardary, 2015). Furthermore, administration of synbiotics was found to have beneficial effects on intestinal morphology and nutrient absorption, leading to enhanced performance (Yadav et al., 2016; Bogusławska-Tryk et al., 2021).

Synbiotics have been shown to suppress the growth of pathogenic bacteria by maintaining an acidic environment in the GI tract, through producing pyroglutamic acid and hydrogen peroxide, and by competing with microorganisms for adhesion to the intestinal epithelium (Rafter et al., 2007; Szymańska-Czerwińska and Bednarek, 2008; Frence et al., 2009; Ribeiro et al., 2011). Lowering the pH value of the intestine promotes development of lactose fermenting bacteria, concomitantly inhibiting the growth of harmful bacterial strains (*Escherichia coli*, *Clostridium*) and reducing the amount of detrimental metabolites they produce (e.g. amines, ammonia). Furthermore, synbiotics attenuate the activity of intestinal enzymes such as β-glucosidase, β-galactosidase, and β-glucuronidase. Indeed, elevated levels of these enzyme is indicative of the proliferation of pathogenic microorganisms in the GI tract (Żary-Sikorska and Juśkiewicz, 2007).

Glucans and α-mannans isolated from the walls of bacteria and yeast have immunomodulatory and antibacterial properties (Newman and Newman, 2001). This is due to the ability of mannans to stimulate the growth and activity of beneficial intestinal microflora whilst limiting the growth of pathogenic microflora such as *Escherichia coli* and *Salmonella* species (Newman, 1994).

Postbiotic compounds responsible for pathogen inhibition include bacteriocins and organic acids (Kareem et al., 2014). Bacteriocins are synthesized antimicrobial peptides that exhibit bacteriostatic or bactericidal properties. Kareem et al. (2014), Mariam et al. (2014), Ołdak and Zielińska (2017) and Ołdak et al. (2020), found that postbiotics extracted from different *Lactobacillus* species inhibited pathogenic Gram-positive and Gram-negative bacteria, including *Listeria monocytogenes*, *Salmonella enterica*, and *Escherichia coli*. Additionally, numerous publications have demonstrated that postbiotics derived from the *Lactobacillus rhamnosus* GG strain have a positive effect on *Helicobacter pylori* therapy (Oh and Jung, 2015; Westerik et al., 2018; Asgari et al., 2019; Keikha and Karbalaei, 2021).

Immune system stimulation

The presence of specific beneficial bacteria supports the correct development and function of the immune system, which improves animal health and the quality of final products. On the other hand, disturbing the balance between beneficial and harmful microorganisms has a negative impact on the health and overall performance of the animal (Mizak et al., 2012; Pickard et al., 2017; Anwar et al., 2019; Alagawany et al., 2021; Yousaf et al., 2022). Thus, postbiotics may contribute to health by providing specific physiological effects. Although the exact mechanisms are still to be elucidated they have been shown to play a role as antibiotic, anti-inflammatory, anti-diabetic, anti-diarrhea, and anti-carcinogenic agents (Aguilar-Toalá et al., 2018).

Immunostimulants, also known as immunomodulators or augmenters, are feed supplements derived from plants, bacteria, fungi and yeasts. Strong immunostimulatory properties are demonstrated mainly by β-glucans and mannans isolated from bacteria and yeasts. They can react directly and indirectly with pathogens, as well stimulating cellular and humoral immunity (Pelizon et al., 2005; Kogan and Kocher, 2007). Numerous reports (Rafter et al., 2007; Gibson and Roberfroid, 2008; Frence et al., 2009; El-Banna et al., 2010) have demonstrated a beneficial effect of symbiotic supplementation on immune system function and immunomodulation. This was achieved by increasing the numbers of acidifying bacteria and activating the lymphoid tissue of mucosal membranes. Other effects of synbiotic supplementation include apoptosis and proliferation of large intestine epithelial cells, increased passive diffusion of ions between cells, and changes in morphometric characteristics of the intestines (Awad et al., 2009; Villagrán-de la Mora et al., 2019; Csernus and Czeglédi, 2020; Zheng et al., 2021; Fathima et al., 2022). Histological studies have also highlighted their effect on the growth of intestinal villi and multiplication of crypts, the latter of which is a site of antibacterial immune agent and endocrine factor production. The mucosal immune system has the ability to respond to potentially pathogenic microbes, invasive pathogens, and microbial products, whilst maintaining a state of tolerance to the diverse and beneficial commensal intestinal microbes (Broom and Kogut, 2018; Zheng et al., 2020). Therefore, the immune system ensures that the microbial load is tolerated, but anatomically contained, while remaining reactive to microbial invasion (Kogut et al., 2020).

The major site of initial contact with environmental antigens is the mucosa-associated lymphoid tissue (MALT), which is composed of diffuse lymphoid tissues and aggregated lymphoid nodules. Based on its anatomical localization it can be further distinguished as: Bronchus-ALT, gut-ALT, nasal-

ALT, larynx-ALT, and conjunctival-ALT, among others. In the GI tract, GALT plays a role in enzyme secretion and absorption of nutrients. It is also the first point of contact with numerous antigens, making it the first natural defensive barrier. The most important task of the GALT is to recognize and distinguish invasive pathogens from beneficial flora and substances that are indispensable for the proper functioning of the body (Singh et al., 2018). Additionally, it is a site for excretion of secretory immunoglobulin A antibodies onto the mucosal surface.

After reaching the GI tract, antigen are bound by receptors on the surface of effector cells, including macrophages, neutrophils, T and B lymphocytes, and monocytes. These surface receptors recognize the structure of this compound and when activated trigger a cascade of immune responses. Immune cells stimulated in this way produce significant amounts of cytokines (the so-called cell hormones, pro-inflammatory mediators), which are directly responsible for the stimulation and multiplication of cells involved in the immune response. Among these cytokines is interleukin 1 (IL-1), which plays a key role in the development of immune responses through activation of macrophages and the stimulation of T lymphocytes to release further cytokines such as IL-2 and IL-6. This ensures that if antigens are present, such as pathogenic microorganisms, they will be recognized and attacked by the already stimulated macrophages (cellular response). Additionally, stimulated T lymphocytes may inhibit the reaction of the gastrointestinal mucosa tissue to the antigen, enhancing its integrity and promoting better feed conversion. However, T lymphocytes can also display cytotoxic properties through capturing and neutralizing various toxins. Finally, B lymphocytes stimulate the immune system to produce antibodies to initiate a specific humoral immune response (Davis, 2004; Broadway et al., 2015; Naquid et al., 2015; Roselli et al., 2017).

Microbiome as an additional immune organ

Functional preparations used to supplement feed have biogenic properties that result in direct stimulation of the host's immune system to activate and produce cellular and humoral responses. Furthermore, additives can influence the host immune system by balancing the microbiome, which is considered to be an additive immune organ. One can expect increased resistance to stress and shorter recovery time after illness. Stress, both psychological and physiological, can disturb the balance of the gut microflora in animals, leading to increased susceptibility to intestinal infections. Indeed, some studies carried out in mice have shown that the microbial composition in the cecum was altered in response to stress. Subsequent research has indicated that feeding pro- and prebiotics reduced the impact of various stress conditions (Juśkiewicz et al., 2007; Rafter et al., 2007; Ribeiro et al., 2011; Mizak et al., 2012; Mohammed et al., 2021). Likewise, a lack these supplements in feed can have a negative impact on the gut microbiome and result in impairment of the immune system (Sudo et al., 2004; Anwar et al., 2019; Vallianou et al., 2020).

Indeed, the gut microbiome was termed a new organ system due to the microorganisms' specific biochemical interaction and systemic integration with the host (Anwar et al., 2019). According to Riccio and Rossano (2020), this term has been misused many times, as the gut microbiota is a very complex entity that does not fit with the other organs of the body. As such, they referred to the gut microbiota as a foreign environmental agent that has adapted itself to the host and been accepted by the host over the course of evolution. This relationship between host and microbiome was characterized as symbiotic beneficial. Therefore, further research is needed before defining the microbiota as an immune organ or as a commensal.

Much research has characterized microbial communities from different parts of the host body that demonstrate host-microbiome interplay and microbial interrelationships. Some adaptive mechanisms have become common to the host and the microbiota, and they are mutually beneficial, though many other mechanisms have certainly remained independent (Riccio and Rossano, 2020). Communication between microbiota and the immune system is mediated by the interaction of bacterial components with pattern recognition receptors expressed by intestinal epithelium, as well as various antigen-presenting cells, resulting in activation of both innate and adaptive immune responses (Kogut et al., 2020). The microbiota is required for intestinal immune development and plays important roles in the development of major components of the host's innate and adaptive immune response. Meanwhile, the immune system orchestrates the maintenance of key features of host-microbe symbiosis (Zheng et al., 2020). This ensures that the intestinal immune and immune responses work together to prevent bacteria from breaching the intestinal barrier.

Postbiotics stimulate the gut microbiome and support the immune function of the gut, with bioactive components derived from probiotics and postbiotics having a protective role in intestinal barrier function similar to live probiotics. Indeed, they increase the expression of the gene responsible for intestinal mucin production, which protects the intestinal barrier from injury caused by lipopolysaccharide and tumor necrosis factor alpha (Gao et al., 2019).

Microbes of the genus *Lactobacillus* are one of the most important in the GI tract, as they exert a substantial effect on immune system function (Abdo et al., 2019; Belkina et al., 2021). Many studies carried out in this area have recorded development and transition of probiotics to pharmabiotics, which are drugs based on bacteria with classical probiotic properties but with an identified active component(s) and with a specific mechanism of action (Oleskin and Shenderov, 2019; Belkina et al., 2021). The role of the microbiome in various diseases, including psychiatric, oncologic, autoimmune and infectious, has been described in the medical literature. Lactobacilli-based drugs are considered psychobiotics, probiotics exhibiting antioxidant potential, and immunobiotics (Levy et al., 2017; Belkina et al., 2021). The research conducted by Berer et al. (2011) indicated that the normal flora was necessary for the induction of autoimmune diseases.

Conclusions

Many products and preparations from feed additives, as well as strategies for their administration, have been widely investigated following the withdrawal of antibiotic feed supplements and the use of medical zinc oxide in animal production. Most of this work has been satisfactory and promising, though results are seldom consistent. This is perhaps due to variability in the environment in which animals live, the feed used, maintenance and management of animals and feed, as well as the age and physiological status of the animals used. Therefore, it has proven impossible to suggest/chose the optimal preparation or administration strategy, meaning that decisions must rely on individual circumstances of use.

Defense mechanisms have developed in the body to protect the intestinal mucosal membrane, maintain allostasis, and activate the immune system in response to potentially disease-causing agents. Furthermore, it is widely accepted that changes in the qualitative and quantitative composition of the intestinal microflora can lead to disease. Synbiotics are a functional component of the diet that have tremendous potential to improve the microenvironment of the alimentary tract and confer benefits to consumers.

Probiotics administered in combination with prebiotics are helpful in the treatment of food allergies, diarrhea, rotavirus infections and inflammatory bowel disease, among other things. Some probiotic strains also exhibit antimutagenic activity, with research indicating their potential for use in cancer therapy. Increasing interest in synbiotic supplementation will contribute to a better understanding of numerous defense mechanisms in the body triggered by probiotics and prebiotics.

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