Ann. Anim. Sci., Vol. 23, No. 2 (2023) 289–313 *DOI: 10.2478/aoas-2022-0057*

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BIOACTIVE COMPOUNDS, ANTIBIOTICS AND HEAVY METALS: EFFECTS ON THE INTESTINAL STRUCTURE AND MICROBIOME OF MONOGASTRIC ANIMALS – A NON-SYSTEMATIC REVIEW*

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Abstract

The intestinal structure and gut microbiota are essential for the animals' health. Chemical components taken with food provide the right environment for a specific microbiome which, together with its metabolites and the products of digestion, create an environment, which in turn affects the population size of specific bacteria. Disturbances in the composition of the gut microbiota can be a reason for the malformation of guts, which has a decisive impact on the animal's health. This review aimed to analyse scientific literature, published over the past 20 years, concerning the effect of nutritional factors on gut health, determined by the intestinal structure and microbiota of monogastric animals. Several topics have been investigated: bioactive compounds (probiotics, prebiotics, organic acids, and herbal active substances), antibiotics and heavy metals (essential minerals and toxic heavy metals).

Key words: bioactive compounds, heavy metals, intestine structure, microbiome, monogastric animals

The optimum health status of an animal is largely determined by the proper function of its gastrointestinal tract, that is, morphological integrity of guts and the correct population size and composition of the gut microbiota (Diaz Carrasco et al., 2019). Intestinal epithelium serves as a place where digestive enzymes are produced and nutritional components are absorbed. In addition, it forms a physical barrier against many dietary antigens (Tomaszewska et al., 2012). Intestinal villi are covered with enterocytes, which originate from the crypts. The mucus produced by crypt cells separates the gut epithelium from microbiota and protects the intestinal mucosa against gastrointestinal juices, pathogens and physicochemical damage (Bansil and Turner, 2018). The mucus contains mucins, antibacterial enzymes and antibodies forming the gut's first protective barrier (Melhem et al., 2021). Maintaining the proper morphology and structural integrity of the intestines is necessary to prevent the translocation of gastrointestinal bacteria (Wu et al., 2016).

The microbiome consists of all types of bacteria (commensal, symbiotic and pathogenic) forming the microecosystem of the gastrointestinal tract. Microbiome modulation is one of the most prospective new strategies aimed at improving the health status and animals' performance (Rebersek, 2021). However, the diversity of probiotic properties in a complex intestinal ecosystem makes it difficult to identify the relationship between specific functions of various bacterial strains and the animal's health status, but studies corroborate the potential of *Lactobacillus* to regulate the function of the immune system, improve the digestive capacity of intestines and to maintain balance in the pigs' gut microbiota (Valeriano et al., 2017). It results from the action of *Lactobacillus* sp. which positively influences the population size of probiotic bacteria by the production of lactic acid, which reduces the pH of the chyme (Yang et al., 2018). The animals' diet has also an essential influence on the composition of the gut microbiome. Certain dietary components stimulate the development of lactic acid bacteria and inhibit the growth of pathogenic bacteria, notably *Escherichia coli* (e.g., probiotics, prebiotics, phytobiotics, organic acids, and minerals); other (e.g., xenobiotics) can disturb the proper proportions in the microbiome's composition. The gut microbiota is essential for the health, and thus has an influence on performance. This review aimed to analyse information available in scientific literature, published over the past 20 years, concerning the effect of nutritional factors in the diet of monogastric animals on their gut health, determined by the intestinal structure and microbiota. Contrary to similar reviews, the presented review is not

*This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

limited only to livestock animals, but also presents the results obtained in experimental works carried out on monogastric laboratory animals (rat, mouse), which can be considered as preliminary studies for products that can be introduced as feed additives in livestock animal nutrition.

Information search strategy

The review and analysis of information available in the world scientific literature were conducted in February and March 2022 using the PubMed, Scopus, Web of Science and Google Scholar databases. The databases were searched according to keywords: "animal", "diet", "gastrointestinal tract", "gut structure", "microbiome", and "supplements". The search resulted in 5689 records, so – following an analysis of the titles and abstracts of scientific publications – the time frame was narrowed to the years 2002–2022, and the terms "antibiotics", "heavy metals", "herbs", "organic acids", "phytobiotics", "prebiotics", and "probiotics" were used as the keywords. The result was 798 hits. After the abstracts had been read, the publications were initially verified and, following analysis of the whole works, the most relevant were selected, and ultimately 237 were used, including 182 original research and 55 review articles.

Significance of the proper intestinal structure and microbiome for the organism function

The mucus barrier of the gastrointestinal tract ensures the physiological stability and protects against exogenous factors modulating the activity of the immune system and controlling the transit of beneficial and toxic substances through the epithelial barrier (Corfield et al., 2000; Herath et al., 2020). In response to antigens present in the chyme, the immune system secretes immunoglobulins, as well as triggers specific responses of macrophages, lymphocytes and cytokines, then inflammation occurs which disturbs absorptive and secretive functions (Corfield et al., 2000; Herath et al., 2020; Wiertsema et al., 2021).

The microbiota of the gastrointestinal tract, dynamic community composed of several hundred species of bacteria, mainly anaerobic having a beneficial effect on the host organism and inhibits the development of pathogenic bacteria, is not fully defined (Chen et al., 2022). The species and amount of bacteria differ depending on the animal's species, age, section and pH of the gastrointestinal tract and on the nutritional and environmental factors (Luise et al., 2020). The microbiota is important since it affects the animal's immunity, which has an influence on its health, as demonstrated by comparative studies involving animals kept in a conventional and in a sterile environment (Luczynski et al., 2016; Gabay et al., 2020; Larsen et al., 2021). Chemical components taken with food provide the right environment for a specific microbiome which, together with its metabolites and the products of digestion, create an environment, which in turn affects the population size of specific bacteria (Lazar et al., 2018). At the same time, commensal bacteria compete with the host for nutrients, produce toxic metabolites, affect the guts' morphology and trigger a continual immune response in the gastrointestinal tract, which undoubtedly has a negative impact on the animal health and performance. The pH in the stomach serves as an ecological filter playing a crucial role in limiting bacteria, so it is essential to shaping the composition of the whole intestinal microflora (Beasley et al., 2015). The most common factor leading to dysbiosis and disturbances in the immune homeostasis is gut infections caused by parasites, viruses and bacteria.

Disturbances in the composition of the gut microbiota can be a reason for the malformation of guts, which has a critical impact on the animal health. An excessive population size of *Clostridium perfringens* of A/G type in the small intestine causes necrotic enteritis in poultry aged 2–6 weeks (Lee and Lillehoj, 2022). Toxins produced by these bacteria damage the intestinal wall; in a sub-clinical form they lead to decreased feed intake and digestive disorder, and in a clinical form they cause up to 50% of birds' mortality in 24 hours (Uzal et al., 2014; Caly et al., 2015; Tsiouris, 2016; Broom, 2017). It is assumed that the main virulent factor is NetB toxin, heptameric protein encoded by plasmid, although some scientific evidence implies that other toxins take part in the pathogenesis of necrotic enteritis (Lee and Lillehoj, 2022). Ulcerative colitis is a disease caused by *Clostridium colinum*, with a mortality rate reaching up to 100% in several days (Radi, 2004). A characteristic feature is ulceration along the gastrointestinal tract: the duodenum, the jejunum, the ileum and the cecum; it often concurs with peritonitis and multifocal necrotic hepatitis. The imbalance of the intestinal microflora due to the abuse of antibiotics, a deficiency of nutrients and/or an infection with the protozoans *Eimeria* spp. is associated with the growth of and colonisation by *Salmonella* and *Clostridium* strains in the gastrointestinal tract, which increases the susceptibility to various types of diseases (Madlala et al., 2021; Wickramasuriya et al., 2022). The infection with *Eimeria* destroys the cells of the epithelial barrier, which increases intercellular permeability and the outflow of nutrients and impairs the digestion and absorption of proteins (Leung et al., 2018; Nabian et al., 2018). Gut damage due to colonisation by *Eimeria* is also associated with multiple disorders in the composition of intestinal micro-organisms, which fosters the colonisation and growth of other pathogens (e.g., *Clostridium perfringens*), making the infected chicks susceptible to secondary diseases that increase the mortality rate (Madlala et al., 2021). In addition, such conditions give rise to inflammatory cytokines such as IL-1β, IL-10, IL-17A, and IFN-γ promoting proliferation and survival of pathogens (Sand et al., 2016; Wei et al., 2019). An infection with *Salmonella enterica* disturbs the composition of the gut microbiome in the colon and the cecum of pigs where a statistically significant increase in the population size of *Anaerobacter*, *Barnesiella*, *Pediococcus*, *Sporacetigenium*, *Turicibacter*, *Catenibac-*

terium, *Prevotella*, *Pseudobutyrivibrio* and *Xylanibacter* is observed compared to healthy animals (Borewicz et al., 2015). By contrast, histopathology of the intestines of weaned pigs infected with *Salmonella typhimurium* showed epithelial damage together with an increase in polymorphonuclear cells and macrophages, particularly in the jejunum and ileum (Bellido-Carreras et al., 2019).

Effect of nutritional factors on the structure of the intestines and the microbiome

1. Bioactive compounds

Probiotics

Probiotics used with feed can modulate the dynamics of changes in the population of microbes in order to determine the advantage of useful micro-organisms over harmful ones. The probiotic regulation of defensive functions also covers (1) regulation of adhesion of micro-organisms to epithelial cells, (2) regulation of intracellular adhesion, and (3) signalling and transport processes of epithelial cells (Paone and Cani, 2020; Pothuraju et al., 2021). It was demonstrated that certain probiotics can either prevent or minimise the epithelial transport dysfunctions by breaking the inflammatory signalling cascade and reducing the production of chlorides participating in maintaining the electrolytic balance of epithelial cells damaged by diseases (Emge et al., 2016). The use of probiotics to reinforce the protective function of the epithelium in various diseases of the gastrointestinal tract requires precise identification of their efficiency depending on the strain used, disease as well as the age and species of the host. Current research implies that new mechanisms exist that are specific to certain probiotic strains. Selective transport of substances through the epithelial tissue and respective epithelial cells makes use of intracellular connections forming both a barrier and a system of links between cells and tissue spaces. It was observed that certain probiotics increase the expression of epithelial tight junction proteins, improving the efficiency of its barrier function (Qin et al., 2005).

Some bacteria and their metabolites modulate epithelial transcription in guts in a different way, as revealed by studies on mice (Lukovac et al., 2014). Inclusion of *Clostridium butyricum* bacteria in the diet of weaned piglets increases the height of villi and the depth of crypts, but does not change the population size of the gut microbiome (Casas et al., 2020). The use of probiotic strains such as *Clostridium butyricum* and/or *Enterococcus faecalis* in weaned piglets increased the length of villi and the villi length/crypt depth ratio and reduced the depth of intestinal crypts, while in the large intestine a higher concentration of volatile fatty acids and a beneficial modulation of colonic microflora was observed (Cao et al., 2019; Wang et al., 2019). Probiotic bacteria produce metabolites such as short-chain fatty acids and bacteriocins beneficial to the animal since they reduce the risk of intestinal infections caused by pathogens, which is particularly important for weaned piglets (Yang et al., 2018). Probiotic bacteria cause fermentation; the simplest fermentation is the conversion of sugar into lactate, but when the level of sugar is low, the bacteria are capable of switching to fermentation producing acetate and formate (Van Immerseel et al., 2006). The acidic environment resulting from fermentation suppresses the growth of pathogenic microbes. Lactic acid bacteria suppress the growth and proliferation of pathogenic strains by producing antibacterial metabolites, for example, bacteriocins, lysozyme, short-chain fatty acids, β-hydroxybutyrate and ROS (Ren et al., 2019). In broiler chickens *Lactobacillus johnsonii* strain BS15 enhanced gut development and digestive capability, primarily through increasing the villi height/crypt depth ratio in the ileum, and increasing the level of the epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1) as well as the activity of trypsin and lipase in the jejunum and ileum (Wang et al., 2017 a). *Lactobacillus sp.* included in the diet of broilers increases the transport of glucose and improves absorption of nutrients in guts, which is connected with an improved gut architecture, but has no effect on the intracellular transport properties of the jejunum and colon, which corroborates the idea that this supplement improves maintenance and functioning of the epithelial barrier (Awad et al., 2010). Supplementation of broiler chickens' diet with probiotic strains of *Bacillus* spp. contributed to improvement in the body weight and gut morphology (Li et al., 2019 a). Chicks fed diets containing *Bacillus amyloliquefaciens* strains of 30 or 60 mg/kg showed an increased height of villi, depth of crypts and villi height/crypt depth ratio in the duodenum, jejunum and ileum (Lei et al., 2015). Supplementation of the diet with probiotic yeasts at a dose of 5 g/kg had a positive effect on the growth performance of weaned pigs, which could stem from an improved height of villi and the villi height/crypt depth ratio and a modulated immune response of guts (van der Peet-Schwering et al., 2007; Shen et al., 2009). Probiotic yeasts *Candida utilis* administered with feed improved the villi height/crypt depth ratio in the guts and increased microflora diversity in the cecum, which contributed decisively to decreasing the frequency of diarrhoea in weaned pigs (Yang et al., 2021 a). In rabbits receiving feed with commercial prebiotics and synbiotics the evaluation of the mucosa in the ileum showed that the height and width of villi, the number of villi, the depth of crypts and the villi height/crypt depth ratio were similar and were significantly higher than in rabbits fed with a commercial probiotic (Nwachukwu et al., 2021). Similar results of feeding chicks with a commercial probiotic or a commercial synbiotic were reported by Awad et al. (2009), where both experimental factors increased the height of villi and the villi height/crypt depth ratio in the duodenum and ileum, while the depth of crypts in the ileum decreased, which was directly associated with improved performance parameters of chickens. Gut histomorphometry in piglets orally receiving a probiotic strain *Pediococcus acidilactici* showed that the villi were longer and the crypts were deeper compared to the control group, and that the number of proliferating entero-

cytes was higher (Di Giancamillo et al., 2008). By contrast, Dela Cruz et al. (2019) found that supplementation of a diet with probiotics (*Bacillus subtilis, Enterococcus faecium*, *Bacillus subtilis* or a blend of *Enterococcus faecium* + *Bifidobacterium* spp. + *Pediococcus* spp. + *Lactobacillus* spp.) had no significant influence on gut morphometry (height of villi and depth of crypts in the duodenum, jejunum and ileum).

Lactobacillus occurs commonly both in the proximal and the distal section of the gastrointestinal tract of pigs, and forms colonies immediately after birth. A positive impact of *Lactobacillus* strains on the gut microbiome and intestine structure was also observed for broiler chickens (Lei et al., 2015; Wang et al., 2017 a). Similar results were obtained for rabbits which, after the use of *Clostridium butyricum,* showed an increase of the population size of useful bacteria (Liu et al., 2019 a). Early-life colonisation of guts with *Lactobacillus rhamnosus* GG has a long-lasting positive effect on health and suppresses the development of gut cancer in mice (Liu et al., 2022). In turn, *Lactobacillus johnsonii* strain BS15 fed to piglets contributed to increasing the population size of *Clostridium, Peptococcus* and *Lactobacillus* and decreased that of *Escherichia coli* (Xin et al., 2020). In poultry, changes in the microbiota colonisation during the first two weeks post-hatch affect the gut function in adult birds and the related feedback between microbiota and cells of the intestinal mucosa (Wisselink et al., 2017). The cecum in poultry is considerably shorter in relation to body length compared to other animals, so the microbiota developing in such conditions must be specially adapted for effective adhesion to the wall of the mucosa and proliferation. In the microflora of the chickens' cecum the population size of *Bacteroidetes* is positively correlated with the content of propionate, butyrate and isobutyrate, while the increase in the content of acetate is positively correlated with the population size of *Firmicutes* bacteria (Wang et al., 2017 b). A blend of probiotic micro-organisms added to broiler chicken feed had a beneficial effect on gut morphology and improved the status and composition of the gut microbiota: the population size of pathogenic bacteria from the *Firmicutes*, *Euryarchaeota* and *Ruminococcus* class significantly decreased, while the population size of bacteria from the *Actinobacteria* and *WPS-2* increased (Ye et al., 2021).

The effects of probiotics can be modified though the administration of other supplements. For example piglets orally receiving a mix of a probiotic (1.25×10^9 CFU/day) and zinc (2000 ppm/day) showed the presence of stem cells at crypt base and elongation of the enterocyte microvilli in the small intestine, which can suggest an increased capacity to absorb nutrients and efficient resistance (Kalita et al., 2021). On the other hand, weaned pigs administered 2500 ppm of zinc oxide and/or a commercial mix of benzoic acid and probiotics (*Bacillus licheniformis*, *Bacillus subtilis* and *Enterococcus faecium*) showed that zinc oxide administered alone had a stronger influence on the composition of the microbiota, although the microbiota of the ceacum in both groups of piglets was dominated by *Firmicutes*, followed by *Bacteroidetes* bacteria (da Silva et al., 2021).

In Table 1 are presented selected probiotics compounds influencing the microbiome composition of monogastric animals.

Prebiotics

Prebiotics are the ingredients of feed having a positive effect on the welfare and health of an animal through selective stimulation of the intestinal microflora's growth and/or activity, thanks to which they also affect the gut structure (Bogusławska-Tryk et al., 2021). Supplementation of the diet with a small dose of chitooligosaccharides (30 mg/kg) decreased the height of villi in the duodenum and jejunum of weaned pigs (Liu et al., 2008; Xiong et al., 2015). In addition, it was found that supplementation with chitooligosaccharides at this level can trigger an immune response and oxidative stress in the small intestine and disturb the integrity of the intestinal barrier in young piglets. Inulin added to the diet of broiler chickens increased the height of villi in the duodenum, the width of villi and the villi height/crypt depth ratio and decreased the height of villi and depth of crypts in the jejunum and ileum (Awad et al., 2011). Some prebiotics have a positive effect on gut health due to selective stimulation of intestinal bacteria, including *Bifidobacteria* (Petersen et al., 2010). It was demonstrated that indigestible oligosaccharides reduced an inflammatory condition in experimental colitis in rat model study (Koleva et al., 2014). In addition, in rats supplemented with oligosaccharides changes in microbiota (an increased share of *Bifidobacterium* and *Enterobacteriaceae* and a decreased share of *Clostridium* cluster IV) as well as higher concentrations of short-chain fatty acids in the cecum content were observed. The study on transgenic HLA-B27 rats with colitis showed that the use of long-chain inulin and oligofructose in their diet decreased the concentration of interleukin Il-1β and increased that of the transforming growth factor β (TGF-β) in the cecum; at the same time, the population of *Lactobacillus* and *Bifidobacterium* in the cecum increased (Hoentjen et al., 2005). Fructooligosaccharides administered to Wistar rats with induced inflammatory bowel disease reduced the symptoms of an inflammation (Lara-Villoslada et al., 2006). This study demonstrated that oligosaccharides are fermented in the upper sections of the large intestine, but their prebiotic effect extends to distal parts of the large intestine, which has a positive effect on the inflammation of the large intestine. Finally, caramel enriched with prebiotic difructose dianhydrides (DFAs) fed to colitic rats decreased the level of inflammatory cytokines in the colon, the tumour necrosis factor alpha (TNF-α) and interleukin IL-1β (Arribas et al., 2010). In the feces of weaned pigs receiving chitooligosaccharides with feed of 100 and 200 mg/kg an increased count of *Lactobacillus* and a decreased count of *Escherichia coli* bacteria was found (Liu et al., 2008). In the large intestine of piglets receiving a prebiotic (oli-

gofructose), probiotic or synbiotic the total count of *E. coli* bacteria was lower, whereas in the large intestine and in the ileum the population of *Bifidobacteria* was larger compared to the control group (Shim et al., 2005). Supplementation of piglet feed with β-glucan improved gut morphology and contributed to balancing the microbiota and enhanced the concentration of fatty acids in the colon (Luo et al., 2019).

In Table 2 are presented other selected prebiotics influencing the microbiome composition of monogastric animals.

Organic acids

Organic acids and their salts play an important role, in particular in ensuring gut health and increasing the growth performance of livestock animals. The main mechanisms allowing organic acids to improve the animals' performance and health are related to the regulation of pH of the gastrointestinal tract and the improvement of intestinal digestibility and utilization of minerals (Luise et al., 2020). The immediate effect of organic acids on bacterial cells is associated with their ability to permeate through the cell membrane, where the acid is dissociated and the pH of the cytoplasm is reduced, which in turn inactivates bacterial enzymes: decarboxylase and catalase (Lückstädt and Mellor, 2011; Luise et al., 2020). To restore the balance and the normal pH of the cytoplasm, the cell is forced to use energy to expel protons out across the membrane via the H^+-ATPase pump. Expelling protons leads to an accumulation of acid anions in the cell, which inhibits intracellular metabolic reactions, including the synthesis of macromolecules, slows down their growth and disrupts internal membranes (Luise et al., 2020; Lückstädt and Mellor, 2011).

Table 1. Influence of selected probiotics on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
Clostridium butyricum or *Enterococcus faecali*	6×10^9 CFU *C. butyricum* per kg and 2×10^{10} CFU *E. faecalis* per kg	↑ *C. butyricum*	Colon	Weaned piglets	Wang et al. (2019)
Bacillus, Lactobacillus, Pediococcus	1 to day 42 – 0.2% *Bacillus, Lactobacillus* and *Pediococcus*-based probiotic fermented products; from day 43 to day 76 – 0.15% probiotic fermented products	*Bacteroidetes* positively correlated with content of propionate, butyrate, and isobutyrate, whereas an increase in acetate content positively correlated with *Firmicutes*	Cecum	Newborn male chickens	Wang et al. (2017 b)
Candida utilis	Basal diet + 1 mL 1×10^9 CFU/ml *C. utilis* in 0.85% saline; basal diet + YSE (120 mg/kg) 1 ml of 0.85% saline; basal diet + 120 mg/kg YSE + 1 ml 1×10^9 CFU/ml *C. utilis* in 0.85% saline	↓ *Proteobacteria*, ↓ *Actinobacteria,* ↑ *Verrucomicrobia*	Cecum	Weaned piglets	Yang et al. (2021)
B. subtilis	*Bacillus coagulans* TBC169, *B. subtilis* PB6, and *B. subtilis* DSM32315 with a dosage of 1×10^9 CFU/kg	*B. subtilis:* ↑ *Pseudomonas*, ↑ *Burkholderia*, ↑ *Prevotella* *B.subtilis* DSM32315: ↑ *Clostridiales*	Jejunum	Broiler chickens	Li et al. (2019 b)

Table 2. Influence of selected prebiotics on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
Oligosaccharides	Fructo-oligosaccharides or isomalto-oligosaccharides 8 g/kg	↑ *Bifidobacterium* spp., ↑ *Enterobacteriaceae* family, ↓ *Clostridium* cluster IV	Cecum	Rats	Koleva et al. (2014)
Oligofructose	Combination of chicory-derived long-chain i in-type fructans and short-chain inulin fraction oligofructose in a mixture of 1:1 in their drinking water at a dose of 5 g/kg body weight	↑ *Lactobacillus,* ↑ *Bifidobacterium*	Cecum, colon	Rats	Hoentjen et al. (2005)
Fructooligosaccharides	Fructooligosaccharides 50 g/kg	↑ *Lactobacillus,* ↑ *Bifidobacteria*	Feces	Female Wistar rats	Lara-Villoslada et al. (2006)
Chitooligosaccharide	Chitooligosaccharide 100, 200 or 400 mg/kg; chlortetracycline 80 mg/kg	↑ *Lactobacillus*, ↓ *Escherichia coli*	Feces	Weaning pigs	Liu et al. (2008)
β-glucans	Basal diet + 50 mg/kg addition of high (2000 kDa) or low (300 kDa) molecular weight β-glucan	↑ *Bifidobacterium*, ↑ *Bacillus* (β-glucan 2000 kDa)	Feces	Weaned piglets	Luo et al. (2019)
Oligofructose, probiotics, synbiotics	Basal diet + 0.2% oligofructose, basal diet+0.3% probiotics or 0.5% synbiotics; basal diet + 0.2% oligofructose + 0.3% probiotics)	↑ numbers of coli forms, ↑ number of bifidobacteria (oligofructose, probiotics, synbiotics)	Colon, ileum	Suckling piglets	Shim et al. (2005)

The mix of organic acids administered to piglets from day 1 to 28 of their lives considerably increased the villi height/crypt depth ratio in the jejunum and ileum compared to those receiving antibiotics (Ma et al., 2021). Similarly, weaned piglets fed diets containing 1 mg/kg of benzoic acid had longer villi and a higher villi height/crypt depth ratio in the duodenum, longer villi in the ileum and decreased depth of crypts in the jejunum compared to piglets fed the control diet (Wang et al., 2021). Moreover, piglets from the benzoic acid group showed a higher concentration of acetate, propionate, butyrate and all short-chain fatty acids in the ileum or cecum. The mix of organic acid administered to chicks with coccidiosis mitigated pathological lesions in the jejunum, decreased the depth of crypts and increased the villi height/crypt depth ratio (Mustafa et al., 2021). Sodium butyrate administered orally to Cobb broiler chickens that received an intraperitoneal injection of lipopolysaccharide at a dose of 500 µg/kg, inhibited the reduction of the villous height in the duodenum and ileum caused by a stress factor (Xiong et al., 2018). Other researchers also reported a positive impact of butyrate supplementation to pregnant sows on the structure of the small and large intestine of their offspring (Dobrowolski et al., 2021; Tomaszewska et al., 2022, 2023). Zinc lactate is another agent having a positive effect on gut structure. Its use in broiler chicken feeding increased the height of villi in the duodenum and ileum and decreased the villi height/crypt depth ratio in the jejunum compared to the control group (Long et al., 2022).

Oral administration of benzoic acid (1 mg/kg) to weaned piglets altered the composition of the microbiome: reduced the population size of *Streptococcus* and *Escherichia-Shigella* and increased that of *Lactobacillus* (Wang et al., 2021). In a study by Kluge et al. (2006), benzoic acid added to piglet feed reduced the count of aerobic, anaerobic, lactic acid bacteria and Gram-negative bacteria in the stomach, reduced the count of Gram-negative bacteria in the duodenum, and reduced the count of aerobic bacteria in the ileum, which was dosage-dependent. Sodium butyrate included in the diet of lactating sows improved the growth rate of weaned piglets and showed potential benefits to the health of gut microbiota: increasing the population size of useful bacteria such as *Oscillospira, Blautia* and *Turicibacter*, and decreasing that of *Veillonella* and *Sarcina* (Wei et al., 2021). Even small doses of butyrate down-regulate the expression of invasion genes in *Salmonella* spp., because bacteria that are unable to decrease intracellular pH accumulate organic acid anions in accordance with the pH gradient across their cell membranes (Van Immerseel et al., 2006). In turn, propionate decreases the ability of *Salmonella* spp. to invade epithelial cells, in contrast to acetic acid (Van Immerseel et al., 2006). A promising solution is designing a diet that will stimulate the production of organic acids in the cecum, which can facilitate controlling *Salmonella* spp., and at the same time is easier and more cost-effective compared to acids added to feed or drinking water.

Antibacterial activity of organic acids introduced into the gastrointestinal tract potentially depends on many factors, including the concentration of acids in the guts, the place of action of the gastrointestinal tract, pH and oxygen levels, species and age of the animal and adequate composition of the population of resident gastrointestinal bacteria (Ricke et al., 2020). In addition, the population of anaerobic bacteria resident in the gastrointestinal tract, becoming more dominant in the lower part of the intestines of monogastric animals as they mature, actively produces organic acids through fermentation which in turn are also potentially antagonistic to transitory pathogens entering the gastrointestinal tract (Ricke et al., 2020). Organic acids have both a bacteriostatic and bactericidal effect. It was found that short-chain fatty acids and their esters can reduce the count of pathogens in guts and simultaneously increase the count of probiotic bacteria (Dibner and Buttin, 2002).

Lower pH of chyme leads to modification of the microbiological composition of the gut, which is primarily a reduction or elimination of acid-sensitive pathogenic bacteria and a selection of acid-resistant bacteria such as lactic acid bacteria, which was observed in the duodenum of piglets fed with 0.9% and 1.8% solution of potassium diformate after 65 hours of experiment (Mroz et al., 2002). In broiler chickens lactic acid reduces pH and delays proliferation of enterotoxic *E. coli* bacteria (Ren et al., 2019). In turn, other authors observed an increase in pH in the small and large intestine for weaned piglets receiving 0.6%, 1.2%, 1.8% or 2.4% solution of formic acid (Luise et al., 2020). Differences in results can be explained by the time between the administration of the acid and the sampling (Luise et al., 2020). Canibe et al. (2005) found that formic acid added to feed has an effect on the gastrointestinal tract mainly through changing the gut environment, which improves the growth performance of growing pigs. It is believed that organic acids in the proximal part of the gastrointestinal tract is a significant factor leading to a decrease in the population size of enterobacteria in the whole gastrointestinal tract. Apajalahti et al. (2009) examined the effect of formic acid on ileal bacterial metabolism in *in vitro* and *in vivo* studies, showing a double effect of formic acid on the gut microbiota of pigs: at concentrations lower than 0.5% it significantly stimulated bacteria, but higher concentration (0.8%) strongly suppressed the growth of bacteria. A study conducted by Luise et al. (2017) aimed to evaluate the effect of two doses (1.4 g/kg or 6.4 g/kg) of formic acid fed over six weeks to weaned piglets on the microbiota composition in the jejunum. The study demonstrated that long-term supplementation of formic acid did not significantly affect the microbiota composition depending on the dose, but greater diversity of the microbiota was observed for animals receiving 6.4 g of formic acid/kg. Despite corroborating the positive effect of formic acid on the gut microbiome composition, no study indicates clearly that formic acid has a positive effect on gut histomorphology (Hernández et al., 2006).

Table 3. Influence of selected organic acids on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
		Organic acids			
Benzoic acid	0%, 0.035%, 0.070% or 0.105% of sodium butyrate combined with 0.5% benzoic acid	↑ *Oscillospira*, ↑ *Blautia*, ↑ *Turicibacter*, ↓ *Veillonella,* ↓ *Sarcina* (basal diet + 0.5% benzoic acid+0.035% sodium butyrate)	Feces	Nursery pigs	Wei et al. (2021)
Organic acids	Organic acids-based formulations (OABF): 1 g OABF/kg diet (OA), avilamycin 2.5 mg active components/kg diet (AV), combination of OA + AV	↑ *Clostridium leptum,* ↑ *Clostridium coccoides*	Cecum	Cobb broilers	Palamidi and Mountzouris (2018)
Fumaric acid	Basal diet + 1, 2 or 3% fumaric acid	↓ concentration of bacteria in the digestive tract	Ileum	Young pigs	Blank et al. (2001)
Organic acid	Combinations of formic, propionic, and medium-chain fatty acids in drinking water or feed (birds inoculated with nalidixic acid-resistant *Salmonella typhimurium*)	↓ *Salmonella* (sequences also declined over time)	Cecum	Broiler chickens	Oakley et al. (2014)
Microencapsulated blends of organic acids	Microencapsulated blends of organic acids (OA) and nature identical aromatic compounds (AC): malic acid + fumaric acid + AC – 2.5 g/kg; calcium butyrate + fumaric acid + AC – 1.7 g/kg; MCFA (capric-caprylic; caproic and lauric acid) + AC – 2 g/kg; MCFA + (calcium butyrate + fumaric acid + citric acid) + AC – 1.5 g/kg	↑ *Ruminococcaceae,* ↑ *Lachnospiraceae*, ↓ *Enterobacteriaceae*, ↓ *Helicobacteraceae*	Ileum	Male Ross 308	Abdelli et al. (2020)
Organic acids	Fumaric acid and an acidifier blend (calcium formate, calcium lactate, capric, caprylic) + (40 ppm) or halquinol (120 ppm)	↓ *E. coli*	Cecum	Weaned piglets	Grecco et al. (2018)
Propionic acids	Formic and propionic acids 0.5 to 1.5%; birds challenged orally on day 3 with 10^4 CFU/ml/bird *S. pullorum.*	↓ *Salmonella pullorum*	Cecum	Layer chicks	Al-Tarazi and Alshawabkeh (2003)
Benzoic acid	Basal diet + benzoic acid at or 10 g/kg; basal diet + potassium diformate at 12 g/kg	↓ aerobic, anaerobic, lactic acid and gram-negative bacteria counts	Stomach	Piglets	Kluge et al. (2006)
Benzoic acid	Basal diet + benzoic acid at 5 or 10 g/kg; basal diet + potassium diformate at 12 g/kg	↓ the number of gram-negative bacteria	Duodenum	Piglets	Kluge et al (2006)
Benzoic acid	Basal diet + benzoic acid at 5 or 10 g/kg; basal diet + potassium diformate at 12 g/kg	↓ the number of aerobic bacteria in a dose-dependent manner	Ileum	Piglets	Kluge et al (2006)
Benzoic acid	Basal diet + 20 mg/kg flavomycin + 50 mg/kg quinocetone AGP; basal diet + 50 mg/kg *Macleaya cordata* extract + 1.000 mg/kg benzoic acid	↓ *Streptococcus*, ↓ *Escherichia-Shigella*, ↑ *Lactobacillus*	Cecum	Weaned piglets	Wang et al. (2021)

Administration of a 1.1% mix of organic acids: acetic, propionic, phosphoric, citric and lactic acid decreased the count of *E. coli* in the feces as early as the fourth day post weaning and reduced the pH in the colon (Namkung et al., 2004). An experiment was conducted in order to evaluate the effect of four different microencapsulated mixes of organic acids (malic acid + fumaric acid, calcium butyrate + fumaric acid, caprylic acid + caproic acid + lauric acid, calcium butyrate + fumaric acid + citric acid) on gut health in 600 one-day-old Ross 308 male chicks (Abdelli et al., 2020). The study found an improved intestine histomorphology, increased population size of *Ruminococcaceae* and *Lachnospiraceae* and a decreased population size of *Enterobacteriaceae* and *Helicobacteraceae*. A study by Grecco et al. (2018) showed a positive effect of feeding a mixture of acidifiers (calcium formate + calcium lactate) and medium-chain fatty acids (caprylic + caproic) to weaned piglets on the relative weight of the large intestine, the height of villi in the jejunum and the total count of *E. coli* in the cecum. Al-Tarazi and Alshawabkeh (2003) demonstrated that a mixture of formic acid and propionic acid reduced the frequency of occurrence of *S. pullorum* in both the crop and cecum.

A signalling molecule regulating embryonic development and playing an important role in fetal nutrition is 2-oxoglutaric acid (α-ketoglutaric acid). It is a primary source of energy for gastrointestinal epithelial cells which also induces proliferation of intestinal cells (Tomaszewska et al., 2012). An experiment was carried out to examine changes in the morphology of the small intestine damaged due to the prenatal exposure to dexamethasone in piglets supplemented with 2-oxoglutaric acid in which 3 mg of dexamethasone were administered to sows intramuscularly every second day starting on the 70th day of pregnancy until the delivery, and their piglets were supplemented with 0.4 g/kg body weight of 2-oxoglutaric acid over 35 days after birth (Tomaszewska et al., 2012). The study found that 2-oxoglutaric acid eliminated intestinal damage due to the prenatal effect of dexamethasone, increasing rate of cellular proliferation and the count and maturity of lymphocytes in the duodenum and jejunum. By contrast, a study involving laying hens showed that 2-oxoglutaric acid contributed to reducing the length and width of villi, and hence the absorptive surface of the small intestine (Tomaszewska et al., 2020).

Another experiment aimed to determine the effect of different levels of fumaric acid (1, 2 or 3%) included in the diet with a low or high dietary buffering capacity on the concentration of microbiological metabolites and lipopolysaccharides as indicators of the presence of Gram-negative bacteria in the ileum of 14-day-old piglets (Blank et al., 2001). Inclusion of fumaric acid reduced the concentration of lactic acid, ammonia, spermidin and lipopolysaccharides in the ileum, which indicates that fumaric acid added to piglets' diet during the first three or four weeks after weaning decreases the metabolic activity and concentration of bacteria in the gastrointestinal tract.

In Table 3 are presented selected organic acids influencing the microbiome composition of monogastric animals.

Herbal active substances

Herbal extracts and essential oils substantially improve the structure of the intestinal epithelium and the composition of the intestinal microflora. The improved structure of the epithelium is primarily manifested as longer and wider villi and deeper crypts in different sections of the intestines (Tatara et al., 2005 a; Hanczakowska and Świątkiewicz, 2012; Ghazanfari et al., 2015; Tomaszewska et al., 2015 a). By contrast, a positive effect on the microbiome composition refers mostly to suppressing the growth of pathogenic bacteria and stimulating probiotic ones (Fujisawa et al., 2009; Bento et al., 2013; Abu Hafsa and Ibrahim, 2018). Herbal extracts owe such an effect to their active ingredients – phytobiotics. They can affect the gut microbiome composition directly or indirectly through altering the pH in the gastrointestinal tract and the time of passage through the gut; they can also promote the growth of strains beneficial to the animal or/and suppress the growth of pathogenic strains (An et al., 2019). Phenolic compounds present in herbs show an antibacterial and antiviral effect and increase cellular proliferation and tissue regeneration (Tretola et al., 2019; Kaczmarek, 2020). They affect the growth of bacteria by suppressing extracellular microbes' enzymes, depriving the bacteria of substrates needed for their growth or direct impact on the metabolism of bacteria by inhibiting oxidative phosphorylation as well as chelating the ions of metals essential to their development (Sieniawska, 2015). Flavonoids, polysaccharides and saponins can also act like probiotics, promoting the growth of *Lactobacillus, Akkermansia muchiniphila* and *Bacillus* (An et al., 2019).

While it was found that tannic acid, a polyphenolic compound, has an adverse effect on rats' feed intake and their general growth when given in large quantities (Winiarska-Mieczan, 2013), due to antioxidant effect (Gülcin et al., 2010) it has a beneficial effect on the composition of the intestinal microflora. Therefore, the possibility of feeding piglets with microencapsulated tannic acid is being tested. Tannic acid microcapsules improved the morphology of the duodenum, intestinal transport of nutrients and gut microbiota composition compared to the control group (Wang et al., 2020 b).

Essential oils are important aromatic components of herbs featuring an antibacterial, antifungal, antioxidant, genotoxic and anti-inflammatory effect (Bento et al., 2013; Puvaca et al., 2021). The positive effect of essential oils on the microbiome composition comprises stimulation of the development of probiotic bacteria (Li et al., 2020), which inhibits the adhesion of pathogenic

bacteria to epithelial cell walls and decreases intracellular invasion and colonisation by these bacteria (An et al., 2019). In addition, they produce antibacterial metabolites against pathogenic bacteria, e.g. organic acids, short-chain fatty acids, hydrogen peroxide, reuterin, diacetyl and bacteriocins (Tharmaraj and Shah, 2009). Many studies imply that interactions between the mucus barrier and pathogenic bacteria or their toxins trigger oxidative stress leading to damage of the intestinal mucosa and lipid peroxidation (Ali et al., 2021). Therefore, the phytocomponents of herbs, having a strong antioxidant effect (phenolic compounds, saponins, alkaloids, and terpenoids) help in reducing free radicals and maintaining normal intestinal mucosa.

A positive effect of garlic and allicin (allyl 2-propenethiosulfinate) fed to sows over the final 24 days of pregnancy and 28 days of lactation on the development of the piglets' gastrointestinal tract, e.g., the length of the sections of the small intestine, was found (Tatara et al., 2005 b). The most prominent changes in the morphology of piglets' intestinal villi under the influence of garlic and allicin were observed between day 7 and 35 of life (Tatara et al., 2005 a). Similarly, positive results after the use of garlic extract (1 ml or 2 ml/kg body weight daily) and allicin (1.0 mg/kg body weight daily) were recorded when the piglets were reared using an artificial sow (Tatara et al., 2008). The width of villi and the depth of crypts and the thickness of the duodenal mucosa were increased in piglets receiving garlic extract, whereas piglets receiving 2 ml of the extract performed better (Tatara et al., 2008). Dried garlic fed to Ross 308 chicks from the first day post hatch increased the height of villi in the duodenum, jejunum and ileum compared to the control group, and increased the width of villi in the ileum (Rastad, 2020). Positive effects on the width and number of villi were also observed for piglets receiving allicin. It was found that improved nutrition at early stages of postnatal development, as the main intrauterine factor, can be beneficial not only right after birth but can have lifelong consequences leading to permanent changes in the structure, physiology and metabolism of offspring (Tatara et al., 2008). The results of these studies are particularly valuable since rapid changes in the gut microflora as a consequence of weaning and a radical diet change were deemed as factors responsible for histological changes in guts (e.g. villous atrophy) resulting in impairment of digestion and absorption and even diarrhoea. Garlic polysaccharides show anti-inflammatory, antioxidant and immunomodulation properties. Administration of polysaccharides extracted from garlic (200 or 400 mg/kg/day) to mice models with dextran sulfate sodium (DSS)-induced colitis increased colon length, reduced colonic mucosa damage and inhibited the expression of inflammatory factors (IL-1β, IL-6 and TNF-α), as well as improved the composition of gut microbiota (Shao et al., 2020). Raw garlic extract has bactericidal properties due to the content of active ingredients and effectively counteracts many pathogenic intestinal bacteria causing diarrhoea in humans and animals. Garlic turned out to effectively counteract even those strains that developed resistance to antibiotics (Sivam, 2001). Allicin present in garlic shows a strong antibacterial effect against many pathogenic bacteria, including the methicillin-resistant *Staphylococcus aureus* (Fujisawa et al., 2009). It was demonstrated that allicin induces thiol stress in bacteria through S-allylmercapto modification of cysteines (Müller et al., 2016).

An experiment conducted to examine the effect of essential oils of thyme and/or anise included in broiler diets on histological changes in the small intestine found that the structure and efficiency of the small intestine improved (Al-Mashhadani et al., 2013). A mix of essential oils (eugenol, nerolidol, piperine, thymol, linalool and geraniol) also had a positive effect on the laying hens' gut morphology (Arslan et al., 2022). Thyme essential oil positively influenced gut integrity in the duodenum of rabbits (Placha et al., 2013) and in broiler chickens (Placha et al., 2014). However, excessive dosage of thyme essential oil can deteriorate gut integrity, as shown by studies on laying hens (Placha et al., 2010). By contrast, thyme and savory essential oils affect the height of villi in the duodenum, jejunum and ileum, and reduce the depth of crypts, as demonstrated by studies on Japanese quails (Dehghani et al., 2018). Studies involving pigs revealed that a mix of thyme and peppermint essential oils and a plant extract of oregano had a positive effect on the microbiological profile of the large intestine, which was manifested by a significant increase in the count of probiotic bacteria (Ruzauskas et al., 2020). Thymol fed to piglets decreased the count of *Escherichia coli* in the proximal part of the small intestine compared to control piglets (Van Noten et al., 2020).

Ross 308 chicks that received 100, 200 or 300 mg/kg of coriander essential oil for 42 days had longer villi and deeper crypts, reduced epithelial thickness and number of goblet cells in the small intestine, which contributed to increasing the feed conversion rate and chicken weight gain compared to control birds (Ghazanfari et al., 2015). Inclusion of 2% coriander seed powder in broiler diets reduced the population size of *Escherichia coli* compared to the control group; simultaneously, an increased immune response was noted (Hosseinzadeh et al., 2014). Coriander seeds are also effective at smaller doses. A study involving 480 Arbor Acres broiler chickens showed that 0.1%, 0.2% or 0.4% of coriander seed powder fed to them for 42 days reduced the count of *Escherichia coli* and *Clostridium perfringens* in the ileum (Abu Hafsa and Ibrahim, 2018). Similarly, chickens receiving oil of coriander showed lower levels of *Escherichia coli* in the cecum compared to control treatment (Ghazanfari et al., 2015). Coriander essential oil, primarily because it contains thymol, shows antimicrobial activity against *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia*

coli and *Proteus vulgaris* (Bento et al., 2013). While essential oils in the first place stimulate the growth of probiotic bacteria also have antioxidant and genotoxic properties (Li et al., 2020; Puvaca et al., 2021).

Essential oils contained in herbs and spices show an antimicrobial effect, but their use in animal feed is limited since they are quickly absorbed in the upper part of the gastrointestinal tract. Therefore, a study on feeding 50 or 100 mg/kg microencapsulated cinnamaldehyde to Cobb broiler chickens was carried out (Yang et al., 2021 b). The study found a significantly higher villi height/crypt depth ratio in broilers receiving cinnamaldehyde in the duodenum and jejunum. Supplementation of broiler diets with essential oil of cinnamon increased the height and surface area of villi in the duodenum and jejunum, which ameliorated the efficiency of absorption and digestion of nutrients. These results were attributed to the antioxidative activity of cinnamon essential oil (Devi et al., 2018). In the process of digestion reactive oxygen species (ROS) are formed that have an adverse effect on the intestinal mucosa and reduce the length of villi, so the antioxidative effect of cinnamon supports processes dependent on normal gut structure. Furthermore, cinnamon essential oil has a bactericidal and bacteriostatic effect, so it contributes to decreasing the count of intestinal pathogenic bacteria, which also improves gut morphology (Windisch et al., 2008). Cinnamon fed to poultry promotes the growth of useful bacteria such as *Lactobacillus* spp., simultaneously suppressing the growth of *Campylobacter* spp. and *E. coli* in the ileum and cecum (Rashid et al., 2020). *Lactobacillus* spp. is responsible for maintaining balance in the intestinal ecosystem through fermentation and reducing the pH of chyme, which inhibits the growth of pathogenic bacteria (Yang et al., 2021 b). Bioactive cinnamon compounds show antibacterial activity against many pathogenic bacteria (such as *Enterococcus faecalis*, *Enterobacter cloacae*, *Vibrio parahaemolyticus*, *Pseudomonas aeruginosa*, *Salmonella* spp., *Klebsiella pneumoniae*, *Staphylococcus epidermis*, *Staphylococcus aureus*, and *Escherichia coli*), fungi (such as *Rhizopus oligosporus* and *Aspergillus niger*) and yeasts (*Candida albicans*) (Yang et al., 2021 b). Jamroz et al. (2005) observed that the guts of broilers receiving feed supplemented with cinnamaldehyde, carvacrol and capsaicin contained more *Lactobacillus* bacteria and less *E. coli* and *Clostridium perfringens*. However, Pathak et al. (2017) reported that cinnamaldehyde administered to broiler orally had no influence on the total count of *E. coli* and *Lactobacillus* bacteria, though the population size of *Clostridium* and *Salmonella* was smaller in the ileum and cecum compared to the control group. In contrast, *in vitro* studies revealed that after eight hours of fermentation using trans-cinnamaldehyde the concentration of *Clostridium* and *Campylobacter jejuni* was reduced with no impact on the natural intestinal microflora (Johny et al., 2010). Mice receiving feed with cinnamon essential oil showed increased diversity of gut microbiota, a reduced count of *Helicobacter* and *Bacteroides* and an increased count of *Bacteroidales*, as well as bacteria producing short-chain fatty acids (SCFA) (Li et al., 2020). Furthermore, the correlation analysis showed that the level of toll-like receptor 4 (TLR4) and TNF-α was positively correlated with the count of *Helicobacter* and negatively correlated with bacteria producing SCFA.

Studies on broiler chickens receiving green tea powder (0.25%, 0.5%, 0.75% or 1% added to feed) showed an increased diameter of the colon and width of the jejunum compared to control chicks (Liu et al., 2021 b). Another study investigated whether regular consumption of green, black, red and white tea had a protective effect on the guts of adolescent and adult rats exposed to Cd and Pb in feed containing 7 mg Cd and 50 mg Pb/kg for 12 weeks (Tomaszewska et al., 2015 a, b). No major damage to the guts of adolescent rats were observed, which proves the protective effect of teas on these organs. In turn, for adult rats the protective effect of tea on heavy metals action was limited. It was also demonstrated that age-related changes in the morphology of the jejunum of rats can be mitigated by long-term supplementation of green tea extract, which leads to the recovery of the normal histological structure of the intestinal mucosa (Hassan et al., 2017), mainly through inducing a considerable transforming growth factor-β1 (TGF-β1) expression in the jejunal mucosa (Mathew et al., 2017). Chlorogenic acid, an ester of caffeic acid and quinic acid, is a polyphenolic compound occurring, for instance, in tea. Chen et al. (2018) found that chlorogenic acid (1000 mg/kg) fed to weaned piglets decreased the level of inflammatory interleukins in blood serum, increased the height and width of villi and the villi height/crypt depth ratio, which the authors attributed to an improved immune defence and suppressed excessive apoptosis of intestinal epithelial cells. Diets rich in chlorogenic acid are also beneficial in the maintenance of the morphological integrity of guts and selective regulation of gut microbiota. In weaned piglets receiving 250, 500 and 1000 mg/kg of chlorogenic acid an increase in the duodenal villi height and the villi height/crypt depth ratio was observed along with an increase in the population size of *Lactobacillus* and a decrease in the population of *Escherichia coli* in the colon (Zhang et al., 2018). In turn, Chen et al. (2019) found that chickens receiving green tea powder (2% share in a diet) showed greater diversity of intestinal bacteria, which was due to promoting the growth of *Proteobacteria*. However, the population size of potentially pathogenic *Gallibacterium* was observed to be higher than in the control group. Recently, in the course of the progressing studies, many experiments have been conducted that provide strong evidence of the capacity of polyphenols contained in tea to regulate the intestinal flora, as a result of their protective effect on the intestinal mucosa and a preventive and therapeutic effect (Wang et al., 2022).

In Table 4 are presented selected bioactive herbal compounds influencing the microbiome composition of monogastric animals.

Table 4. Influence of selected herbs and herbal active substances on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
Chlorogenic acid	Basal diet containing 250, 500 or1000 mg kg^{-1} chlorogenic acid	↑ *Lactobacillus*, ↓ *Escherichia coli*	Colon	Weaned piglets	Zhang et al. (2018)
Chlorogenic acid	Basal diet + 2% green tea powder; basal diet + 4% mulberry leaf powder	↑ pathogenic *Gallibacterium*	Intestines	Chickens	Chen et al. (2019)
Cinnamon essential oil	Dextran sodium sulfate 3% in the drinking water from day 1 to day 7; dextran sodium sulfate 10 mg/kg body weight ceftriaxone sodium; dextran sodium sulfate – 10 mg/kg or 15 mg/kg body weight cinnamon essential oil	↓ *Helicobacter*, ↓ *Bacteroides*, ↑ short-chain fatty acids (SCFA)-producing bacteria (*Alloprevotella* and *Lachnospiraceae*_NK4A136_group)	Feces	Female KM mice	Li et al. (2020)
Trans-cinnamaldehyde, eugenol, carvacrol, and thymol	Appropriate quantities of TC, CAR, THY, and EUG added to each 10 ml sample of cecal contents to obtain a final concentration of 10, 15, and 25 mM of TC; 10, 50, and 75 mM of CAR or EUG; or 25, 50, and 75 mM of THY for *Salmonella enteritidis*; and 10, 20, and 30 mM of all compounds for *C. jejuni*	↓ *Clostridium,* ↓ *Campylobacter jejuni*	Cecum	Chickens	Johny et al. (2010)
Cinnamaldehyde	AGP (NC + 125 mg enramycin (containing 80 mg active enramycin/g) per kg feed; organic acids (NC + organic acids containing 10% formic acid), 500 mg/kg; essential oil + organic acids (NC + cinnamaldehyde 15% + calcium formate 500 mg/kg feed)	↓ *Clostridium*, ↓ *Salmonella*	Ileum, cecum	Broiler chickens	Pathak et al. (2017)
Capsaicin, cinnamaldehyde, carvacrol	Basal diet + 100 mg/kg plant extract consisting of capsaicin, cinnamaldehyde and carvacrol	↑ *Lactobacillus,* ↓ *E. coli*, ↓ *Clostridium perfringens*	Small intestine, cecum	Hubbard Hi-Y broiler hybrids	Jamroz et al. (2005)
Phytogenic feed additives and organic acids	Basal diet + 40 g/t antibiotic growth promoter; basal diet + 3 kg/t organic acids; basal diet + 3 kg/t phytogenic feed additives; basal diet + 3 kg/t organic acids+phytogenic feed additive combination	↑ *Lactobacillus* spp. ↓ *Campylobacter* spp. ↓ *E. coli*	Ileum, cecum	broiler chickens	Rashid et al. (2020)
Coriander essential oil	Basal diet + 600 mg/kg of a flavophospholipol antibiotic, 100, 200 or 300 mg/kg coriander essential oil	↓ *Escherichia coli*	Cecum	Ross 308 broiler chickens	Ghazanfari et al. (2015)
Coriander seed powder or extract	Basal diet + 750, 1000 or 1250 ppm coriander extract in drinking water	↓ *Escherichia coli* (2% coriander powder form)	Ileum	broiler chickens	Hosseinzadeh et al. (2014)
Thymol or thymol α-D-glucopyranoside	*Origanum vulgare* extract + *Mentha piperita* + *Thymus vulgaris* essential oils	↓ *Escherichia coli*	Proximal part of the small intestine	Weaned pigs	Van Noten et al. (2020)
Origanum vulgare plant extract+*Mentha piperita* and *Thymus vulgaris* essential oils	Basal diet + 986 mg of oregano extract, 3 mg of peppermint essential oil and 7 mg thyme essential oil	↑ number of probiotic bacteria	Colon	Pigs	Ruzauskaset al. (2020)

2. Antibiotics

While a prohibition of the use of antibiotics as growth promoters in livestock production systems in the EU was implemented in 2006, it was decided that antibiotics have to be presented as factors not only influencing microbiome, but also having a potential impact on intestinal morphology. In the study of Smirnov et al. (2005) the administration of growth-stimulating antibiotics to one-day-old Cobb chicks increased the share of *Bifidobacterium* species in the duodenum compared to the control group. It was also found that while antibiotics were not found to affect the thickness of the mucous layer in the guts, the villous surface area was increased in the jejunum, and goblet cell density was greater in the jejunum and ileum. An administration of virginiamycin to Ross 308 chicks for 42 days increased the height and width of the villi in the duodenum, jejunum and ileum compared to the control group (Rastad, 2020). Samples of the jejunum collected from broiler chickens receiving avilamycin on days 1, 3, 7, 21 and 42 of the experiment showed no effect of the antibiotic on the height of the villi and the total count of mesophilic and lactic acid bacteria; however, avilamycin suppressed the growth of *Weisella*, *Enterococcus faecium* and *Pediococcus acidophilus* bacteria and stimulated that of *Pseudomonas* (La-ongkhum et al., 2011). An antibiotic (carbadox/copper sulfate) administered to 24-day-old weaned pigs did not affect the height of the villi and the depth of crypts in the ileum, but the height of the villi in the jejunum increased compared to the control group, which increased the villi height/crypt length ratio (Oliver and Wells, 2013). On the other hand, in chickens that from the 15th day post hatch received drinking water mixed with amoxicillin or enrofloxacin, intestinal morphology and development were not clearly affected compared to the control group. No differences were observed between the villi height/crypt depth ratios and numbers of PAS+ and PCNA+ cells in the duodenum and jejunum (Wisselink et al., 2017).

Numerous studies emphasise the significance of microbial colonisation of the guts at an early stage of life as a condition for the correct development of resistance and the necessity to determine the possibilities of regulating animals' health through nutritional and environmental factors at an early stage of life. Dysbiosis of the gut microbiota at the early stage of life can affect the specific immune response at later stages of life (Simon et al., 2016). Therefore, many studies investigate how the use of antibiotics during the first weeks, post-hatch, affects the response in specific antibodies at later stages of the chickens' life. Antigenic keyhole limpet hemocyanin (KLH) oral immunisation of two-week-old chicks receiving orally ampicillin and neomycin increased the production of antibody response (IgM, IgA, and IgY) two- or three-fold compared to the control group, and the count of *Lactobacillus* in the chickens' feces decreased (Murai et al., 2016). The use of antibiotics temporarily disturbs the microbiological balance, and decreases the diversity and abundance of micro-organisms in the gastrointestinal tract. Administration of 0.8 mg of amoxicillin to one-day-old chicks over 24 hours had a short-term impact on the gut microbiota, however, it influenced mucosal gene expression, which altered biological activity of jejunum for over 2 weeks (Schokker et al., 2017). The use of amoxicillin or enrofloxacin in chicken feeding from day 15 post-hatch over five days initially led to slight modifications in the microbiota composition of the jejunum, but these changes disappeared 16 days after the application of amoxicillin and 27 days after the application of enrofloxacin (Wisselink et al., 2017). Avilamycin was widely used as an antibiotic stimulating the growth of poultry until its use was banned in certain regions of the world. The study on broiler chickens demonstrated that the diversity of bacteria in the ileum was higher in chickens fed with avilamycin than in the control group, contrary to the situation in the cecum; this mainly referred to *Lactobacillus reuteri*, *Lactobacillus crispatus* and *Clostridium* (Choi et al., 2018). In another study young laying hens were orally administered an antibiotic cocktail consisting of vancomycin, neomycin, metronidazol and amphotericin B every 12 hours and ampicillin and colistin in drinking water during the first week post-hatch, followed by ampicillin and colistin in drinking water during the subsequent two weeks (Simon et al., 2016). While fecal microbiota of birds during antibiotic treatment was mainly composed of *Proteobacteria*, primarily *E. coli*, and the fecal microbiota of control birds contained mostly *Firmicutes* bacteria (*Lactobacillus* and *Clostridia* strains), the composition of microbiota of experimental chickens was similar to that of control chickens after two more weeks.

Also in newborn piglets the variability of the environment at an early stage of life has an influence on the gut microbiota composition and the development of the immune system. In a study by Schokker et al. (2014) the piglets received subcutaneous injections of tulathromycin on the fourth day of their life. The antibiotic treatment increased the share of *Bifidobacterium*, *Erysipelotrichi*, *Eubacterium*, *Faecalibacterium prausnitzii* and *Solobacterium moorei* and decreased the population size of *Bacillus* and *Staphylococcus aureus*. Preventive use of antibiotics in the feed efficiently reduced the frequency of diarrhoea in weaned piglets. However, excessive use of antibiotics as preventive or therapeutic drugs in feed leads to the development of drug-resistant bacteria, changes in the intestinal epithelium and leaves residues of antibiotics in the pigs' bodies (Klebaniuk et al., 2018). Ruczizka et al. (2019) evaluated the short- and long-term effect of ceftiofur on the development of fecal microbiota in sucklings and growing pigs (n = 64). Piglets from the experimental group received an intramuscular injection of the antibiotic 12 hours after birth. The administration of ceftiofur disturbed the maturational changes in the fecal microbiome, whereby the effects were sex-specific.

In Table 5 are presented selected antibiotics influencing the microbiome composition of monogastric animals.

Table 5. Influence of selected antibiotics on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
Amoxicillin	Enrofloxacin 5 mg/kg or amoxicillin 11 mg/kg for 5 days	↑ *Lactobacillus reuteri,* ↑ *Lactobacillus crispatus,* ↑ *Clostridium*	Ileum	Broiler chickens	Choi et al. (2018)
Amoxicillin	Enrofloxacin 5 mg/kg or amoxicillin 11 mg/kg for 5 days	↓ *Lactobacillus reuteri,* ↓ *Lactobacillus crispatus,* ↓ *Clostridium*	Cecum	Broiler chickens	Choi et al. (2018)
Avilamycin or probiotic	Avilamycin 5 mg/kg or probiotic 2 g/kg for 14 days	↑ *Bifidobacterium*	Duodenum	Cobb broilers	Smirnov et al. (2005)
Avilamycin	Avilamycin 5 mg/kg	↓ *Weisella*, ↓ *Enterococcus faecium,* ↓ *Pediococcus acidophilus,* ↑ *Pseudomonas*	Jejunum	Broiler chickens	La-Ongkhum et al. (2011)
Ampicillin and neomycin	Ampicillin 0.25 g/l and neomycin 0.5 g/l in drinking water	↓ *Lactobacillus*	Feces	Chickens	Murai et al. (2016)
Tulathromycin	Tulathromycin 0.1 ml	↑ *Firmicutes,* ↑*Proteobacteria,* ↑*Bacteriodetes,* ↑ *Spirochaetes,* ↑ *Actinobacteria,* ↑ *Bifidobacterium*, ↑ *Erysipelotrichi*, ↑ *Eubacterium*, ↑ *Faecalibacterium prausnitzii*, ↑ *Solobacterium moorei,* ↓ *Bacillus*, ↓*Staphylococcus*	Jejunum	new-born piglets	Schokker et al. (2014)
Vancomycin, neomycin, metronidazole, amphotericin-B, ampicillin, colistin	Antibiotic cocktail (vancomycin, neomycin, metronidazole, amphotericin-B) by oral gavage every 12 h; ampicillin and colistin in drinking water for the first week of life; after ampicillin and colistin in drinking water for two more weeks		Feces	Laying hens	Simon et al. (2016)

3. Heavy metals

Essential minerals

Essential non-toxic heavy metals (zinc (Zn), copper (Cu), manganese (Mn), iron (Fe), and selenium (Se)) influence both the gut structure and the microbiome. It is achieved by a complex mechanism including: (1) an antioxidant effect (Zn, Cu, Mn, and Se); (2) bactericidal properties (Cu and Zn) and (3) their key role in bacterial metabolism (Fe, Zn, Cu, and Mn) (Jiao et al., 2017; Winiarska-Mieczan et al., 2021; Pajarillo et al., 2021). A deficiency of Zn is associated with an impaired permeability of the guts and a general deterioration of gastrointestinal health (Koren and Tako, 2020). The antioxidant effect of Zn consists of two mechanisms: protecting protein sulfhydryl groups and reducing the intensity of formation of the hydroxyl radical ·OH from hydrogen peroxide due to an antagonistic effect on redox-active transition metals such as Cu and Fe (Winiarska-Mieczan et al., 2021). Mn and Zn form part of many enzymes, including superoxide dysmutase (SOD), citric acid dehydrogenase and farnesyl pyrophosphate synthase demonstrating a high reduction potential (Winiarska-Mieczan et al., 2021; Zandi and Schnug, 2022). Essential minerals regulate the survival of bacteria by modulating the key metabolic pathways, including through riboflavin biosynthesis and regulation of energy uptake from food (Fe), metabolising carbohydrates, lipids and protein and influencing the replication of DNA (Mn), regulating ribosomal protein expression, maintaining cellular activity and reducing glucose metabolism by suppressing the key glycolytic enzymes, which results in decreased virulence (Zn), affects the metabolism of energy and proteins and the biosynthesis of amino acids (Cu), and mitigates oxidative stress (Cu, Mn, Se) (Dostal et al., 2015; Artym and Zimecki, 2020; Pajarillo et al., 2021). Simultaneously, it was demonstrated that intestinal bacteria, both commensal and pathogenic, develop resistance to trace elements and an accompanying antimicrobial cross resistance (Yazdankhah et al., 2014).

Since the form in which minerals are administered to animals (organic, inorganic) has an influence on how they are absorbed and utilised, a study was made comparing the effect of Cu glycinate chelate (organic) supplemented at different doses (50, 75 and 100% of the daily demand) and standard (100%) dose of copper sulphate ($CuSO_4$, inorganic) on gut health in 12-week-old Wistar rats (Tomaszewska et al., 2016, 2017). The above-mentioned study, based on histomorphometry of jejunal epithelium, found that Cu administered in an organic form covering 100% of the demand thinned the mucosa and submucosa layer and reduced the depth of crypts with no effect on the enteric system in the jejunum, while Cu administered in an organic form covering 75% of the demands had no influence on the morphology of the rats' intestines. Also rats receiving organic Cu (at an amount covering 75% and 100% of the demand) showed an increased amount of young collagen compared to rats receiving sulphate at the standard dose. Concluding, it was found that Cu administered to rats in an organic form with a diet covering 50 or 75% of the demand is less harmful for the intestinal epithelium than when administered at an amount covering 100% of the demands. Copper sulphate ($CuSO_4$) fed

to pigs at an amount supplying 225 mg of Cu increased the height of the villi in the duodenum and decreased it in the jejunum compared to the control, no Cu-supplemented group (Shannon and Hill, 2019). Conversely, in chicken feeding, $CuSO_4$ (30 or 70 mg) contributed to increasing the height of the villi in the jejunum (Levkut et al., 2017). Zinc oxide (ZnO) administered at 380 or 570 mg of Zn/kg of feed improved intestinal immunity and regulated the composition of the microbiota in weaned pigs; the villi in the duodenum were longer, the villi height/crypt depth ratio was higher and the crypts were deeper (Shen et al., 2014). Interestingly, excessive dose of ZnO (2250 mg/kg) was not equally efficient. Supplementation of the fattening pigs' diet with ZnO affected the morphology of the mucosa of the small intestine. The mucosa was found to become thicker, the villi were longer and wider and the crypts were deeper compared to the control group (Li et al., 2001). Similar effect of ZnO was observed in poultry, where villi were longer and the villi height/crypt depth ratio in the duodenum increased when compared to control group (Shannon and Hill, 2019). Similarly, the use of yeasts enriched with Se in the case of weaned pigs exposed to oxidative stress (provoked with diquat) resulted in longer villi and increased the villi height/crypt depth ratio in the jejunum and the cecum; it also decreased the overall ratio of the intestinal epithelial cells' apoptosis compared to piglets not receiving the supplements (Liu et al., 2020).

Fe affects the composition of the gut microbiota through regulation of the uptake of energy from food consumed by the host (Dostal et al., 2015). Bacteria take Fe from food in the gut thanks to transportation via the receptors of iron-bound proteins (transferrin and heme) and through capturing Fe by releasing Fe carriers. Studies show that Fe carriers, for example, the Fe capturing system and the Fe transportation system, are expressed in certain bacteria (Pajarillo et al., 2021). In addition, some bacteria produce hemophore-like proteins that transport the heme using the receptor capture. A strong dysbiosis of the gut microbiota accompanied by a decrease in the content of its main metabolites, observed at very low levels of Fe, can weaken the barrier effect of the microbiota and thus negatively affect gut health, as demonstrated during *in vitro* studies involving rats into whose intestines the human fecal microbiota was transplanted (Dostal et al., 2013, 2014). Supplementation of an Fe-deficient diet of rats with 35 mg Fe/kg significantly increased the population size of the dominant groups of bacteria, mostly *Bacteroides* spp. and *Clostridium* cluster IV compared to the group with zero supplementation (Dostal et al., 2014). In addition, the supplementation of Fe increased the concentration of butyrate in the gut microbiome sixfold compared to Fe deficiency and had no impact on the histological assessment of colitis. The absorption of Fe is stimulated by *Lactobacillus acidophilus*, while it is suppressed by *Bifidobacterium infanti.* In contrast, *Bifidobacteriaceae* synthesise Fe carriers, which leads to the peroxide reduction and decreases the risk of gut diseases (Pajarillo et al., 2021). Fe has an influence on the absorption of Mn, since both metals use the same transporters (Pajarillo et al., 2021). Fe stimulates the growth of *Bifidobacteriaceae*, and Mn – as a cofactor of many cell enzymes – is necessary for the growth of *Lactobacillus* (Artym and Zimecki, 2020).

Mn, although necessary for the correct functioning of the body, is still a heavy metal. Poisoning with Mn can alter the gut microbiota, which was demonstrated in studies on pigs and mice (Chi et al., 2017 b; Peng et al., 2019; Wang et al., 2020 a). Modulation of the gut microbiota with Zn decreases the frequency of diarrhoea as zinc mitigates intestinal damage and reinforces the anti-inflammatory agents and integrity of the mucosa in weaned pigs (Pieper et al., 2012). Moreover, supplementation of the diet with Zn decreases the count of *Enterobacteria*, *Clostridium* cluster XIV and *E. coli*, increases the content of acetate and butyrate and improves the gut function of pigs (Pieper et al., 2012; Kociova et al., 2020). Exposure to high levels of Cu can induce toxicity and trigger the development of resistance to Cu in certain pathogenic bacteria, but, on the other hand, reduce the relative population size of potential pathogens, including *Enterobacter*, *Escherichia* and *Streptococcus* (Villagómez-Estrada et al., 2020; Pajarillo et al., 2021). Long-term exposure to Cr(VI) substantially changes the diversity and composition of the chickens' gut microbiome. Bacterial strains that were dominant in the gut microbiota of chickens receiving Cr(VI) were *Firmicutes* and *Actinobacteria*, while in the control group these were *Firmicutes* and *Bacteroidetes* (Li et al., 2021). The taxonomic analysis of bacteria showed that the relative population size of three classes and seven genera clearly increased, while that of eight classes and thirty genera radically decreased during the induction of Cr(VI). Intestinal bacteria are the body's first front line, converting toxic Cr(VI) into less toxic Cr(III), as demonstrated by studies on Wistar rats that were administered drinking water containing 10 ppm of Cr(VI) over 10 weeks (Shrivastava et al., 2005). Moreover, it was observed that long-term exposure to Cr(VI) promotes the development of colon cancer in mice, which is attributed to modifications in the gut microbiota and the occurrence of oxidative stress (Zhang et al., 2020). In their studies involving mice, Zhao et al. (2022) demonstrated that the pathological effect of Cr(VI) on the microflora of the ileum and cecum can be effectively mitigated by Se treatment. Studies on mice found that intestinal bacteria can compete with the host for Se where its availability is limited (Hrdina et al., 2009). Other research involving mice devoid of the microbiome showed significant differences in the levels of about 70% of the determined metabolites of the gut microbiota, including fatty acyls, glycerolipids, glycerophospholipids and steroids in mice supplemented with Se compared to those not receiving the supplement (Callejón-Leblic et al., 2022). In that study a strong relationship was also found between the metabolites and the profile of intestinal bacteria – in particular the population size of *Lactobacillus* spp. – was higher in mice

supplemented with Se. A beneficial effect of the supplementation of Se on the microbiome's composition was also found by other researchers for mice (Callejón-Leblic et al., 2021) and laying hens (Muhammad et al., 2021).

In Table 6 are presented selected non-toxic essential minerals influencing the microbiome composition of monogastric animals.

Table 6. Influence of essential minerals on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
Copper, mercury	Cu 5 mg/kg body weight ($CuCl_2$); Hg 2 mg/kg body weight ($HgCl_2$); Cu + Hg (Cu 2.5 mg/kg body weight, Hg 1 mg/kg body weight)	↓ *Rikenella*, ↓ *Jeotgailcoccus,* ↓ *Staphylococcus*, ↑ *Corynebacterium* in the group with Cu; ↓ *Sporosarcina*, ↓ *Jeotgailcoccus*, ↑ *Staphylococcus* in the group with Hg and Cu + Hg ↑ *Anaeroplasma* in the group with Cu+Hg	Cecum	Mice	Ruan et al. (2019)
Copper	Cu 5 mg/kg body weight ($CuCl_2$)	↑ *Corynebacterium,*↓ *Staphylococcaceae*, ↓ *Odoribacter,* ↓ *Rikenella,* ↓ *Jeotgalicoccus*	Cecum	Mice	Cheng et al. (2020)
Copper	Cu 5 mg/kg body weight ($CuCl_2$)	↑ *Dehalobacterium*, ↑ *Coprococcus*, ↑ *Spirochaetales*, ↓ *Salinicoccus,* ↓ *Bacillales,* ↓ *Staphylococcus,* ↓ *Lactobacillales*	Rectum	Mice	Cheng et al. (2020)
Copper	$CuSO_4$ (350 ppm) after 30, 60, and 90 days	At the phylum level: ↑ *Proteobacteria*, ↑ *Actinobacteria,* ↓ *Bacteroidetes* At the genus level: ↓ *Rikenellaceae_RC9*, ↑ *Ruminococcaceae UCG-014*, ↑ *Lachnoclostridium, (Eubacterium) coprostanoligenes*	Cecum	Chicken	Huang et al. (2021)
Copper	0.04, 0.20, or 1.00 mg/kg body weight Cu ($CuSO_4$) in 0.9% saline for 15 days	↓ *Firmicutes* to *Bacteroidetes*	Feces	Rats	Dai et al. (2020)
Copper	Cu 5 mg/kg body weight ($CuCl_2$)	↓ *Rikenella*, ↓ *Jeotgailcoccus,* ↓ *Staphylococcus*, ↑ *Corynebacterium*	Cecum	Mice	Ruan et al. (2019)
Copper	Basal diet + CuO NPs at dosage of 2.13 mg/kg of feed (with Cu 1.7 mg/kg)	No effect on microbiota	Feces	Broiler chickens	Sizentsov et al. (2018)
Zinc	ZnO (500, 1000, and 2000 mg of Zn equivalent/kg diet) for 10 days.	↓ *Enterobacteria*, ↓ *Clostridium* cluster XIV, ↓ *E. coli*	Feces	Weaned piglets	Kociova et al. (2020)
Zinc	Zn biofortified wheat (75% Zn wheat based diet, 46.5 ± 0.99 μg Zn/g)	↑ *Firmicutes* (*Lactobacillus Reuteri, Dorea, Clostridiales, Ruminococcus, Lachnospiraceae*)	Small intestine	*Gallus gallus*	Reed et al. (2018)
Zinc	Nano-ZnO (ZnO at a dose of Zn 250 mg/kg body weight); zinc sulfate (0.2 ml zinc sulfate solution at a dose of Zn 250 mg/kg body weight) for 7 weeks	Zinc sulfate increased the proportion of the enteric group. Nano-ZnOs did not affect the intestinal bacterial population (B*ifidobacterium* and *Enteric* groups)	Cecum	Male mice	Wang et al. (2017 c)
Zinc	Nanocomposite of half-fin anchovy hydrolysates (HAHp) and ZnO nanoparticles – daily dose of 1.0 g/kg body weight for 14 days)	↑ *Firmicutes*, ↓ *Bacteriodetes,* ↑ *Lactobacillus,* ↑ *Bifidobacterium*, ↑*Clostridia* class	Feces	Mice	Song et al. (2018)
Zinc	Basal diet + nano-ZnO (ZnO 150, 300, 450 or 3000 mg/kg) for 21 days	↓ *Escherichia coli* (ZnO 450 and 3000 mg/kg)	Cecum, colon, and rectum	Weaned pigs	Pei et al. (2019)
Manganese	100 ppm $MnCl_2$	↑ *Firmicutes* ↓ *Lactobacillus*	Feces	Male mice	Chi et al. (2017)
Manganese	100 ppm $MnCl_2$	↓ *Firmicutes*	Feces	Female mice	Chi et al. (2017)
Manganese	Manganese chloride ($MnCl_2$), 200 mg/l in drinking water	↑ *Firmicutes bacterium ASF500,* ↑ *Faecalibacterium prausnitzii,* ↑ *Ruminococcus,*↑ *Clostridium celatum,* ↑ *Lactobacillus johnsonii,* ↑ *Fusobacterium sp. CAG:815,* ↑ *Clostridium sp. CAG:813,* ↑, *Clostridium sp. JCC,* ↑ *Firmicutes bacterium CAG:475,* ↑ *Clostridium sp. CAG:349*	Feces	Sprague--Dawley male rats	Wang et al. (2020)
Vanadium	Vanadium 10 mg (V10) per kg; basal diet + V10 per kg; V10 + 600 mg tea polyphenols per kg; V10 + 1000 mg tea polyphenols per kg	no influence on the number of *Lactobacillus, Escherichia coli*, and total bacteria	Cecum	Laying hens	Yuan et al. (2016)

Toxic heavy metals

The toxicity of metals is primarily due to their ability of producing reactive oxygen species (ROS) and oxidising proteins and fat building cell membranes, which results in oxidative stress (Winiarska-Mieczan, 2018). Studies involving human Caco-2 cells showed that the intestine is an organ that can take part in the pre-systemic metabolism of inorganic arsenic (As) (Calatayud et al., 2012). The body's inflammatory and oxidative response to exposure to As can be responsible for structural and functional modifications in the mucosal layer, which leads to the loss of the epithelial barrier function (Chiocchetti et al., 2019). Subchronic exposure to As affects the structure of the epithelium, causing the loss of microvilli, structures essential to intestinal absorption and digestion processes, and may change the intestinal homoeostasis, at the same time affecting the intestinal mucosa (Chiocchetti et al., 2018). The effect of chronic exposure of young and adult Wistar rats to cadmium (Cd) and lead (Pb) of 7 mg Cd/kg and 50 mg Pb/kg for 12 weeks on the histomorphology of the jejunal epithelial cells and liver was examined (Tomaszewska et al., 2015 a, b). These experiments demonstrated that exposure to Cd and Pb significantly decreased the thickness of the intestinal mucosa and submucosa and the depth of crypts. In turn, exposure to mercury (Hg) causes degenerative lesions of various sections of the gastrointestinal tract, which in the first place are inflammations and infiltrations, as observed in studies involving mice (Jiang et al., 2018).

Heavy metals that are essential and toxic have an antibacterial effect, which can be beneficial for suppressing growth or killing pathogens, but is also harmful to commensal and useful bacteria forming the gut microbiota (Bist and Choudhary, 2022). The antibacterial activity of heavy metals results from the oxidative stress they induce and can also be based on disturbed gene expression and damage to DNA (Zhou et al., 2008). Exposure of the gut microbiota to toxic metals can affect its composition, depending on the location, microenvironment and the population size of susceptible and/or resistant strains (Giambò et al., 2021). Furthermore, host-related factors such as diet, sex, age and immunity status can have an influence on this interaction (Assefa and Köhler, 2020). It is significant that biotransformations induced by intestinal bacteria such as reduction, oxidation, methylation and demethylation, can modulate the toxicity of metals, as demonstrated in studies involving mice devoid of microflora after six-week oral exposure to Cd and Pb (Breton et al., 2013 a). In turn, studies on Caco-2 cells suggested that oral uptake of heavy metal binding bacteria *Lactobacillus* spp. can be a simple and efficient method of reducing the amount of heavy metals absorbed with food (Daisley et al., 2019; Jiang et al., 2018). This is probably due to the protective role of the intestinal barrier (associated with the mitigation of oxidative stress induced by heavy metals and the chelating properties of probiotics) and the modulation of the inflammatory condition due to the interaction of the MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling cascades (Zhai et al., 2016; Jiang et al., 2018). Bolan et al. (2021) confirmed that the permeability of the guts to toxic metals (As, Cd, Pb, Hg) is reduced under the influence of intestinal micro-organisms and chelating agents, using an *in vitro* intestinal epithelium model made of Caco-2 cells.

Gokulan et al. (2018) investigated the relationship between short-term exposure to As and the composition of the gut microbiome and the immune status of intestines in adult and young CD-1 mice. Single doses of As administered to young mice gave rise to different populations of bacteria, which demonstrates that exposure to As at an early stage of life can have long-lasting consequences for the development of a healthy gut microbiota. In turn, repeated exposure increased the population size of bacteria resistant to As and induced the methylation of As for detoxification. A decreased count of bacteria engaged in transforming protein to butyrate, together with signs of immune modulation was also found. Studies involving mice showed that exposure to As and Cd significantly altered the gut microbiome and metabolome through their influence on bile acids, amino acids and taxons associated with metabolic health (Lu et al., 2014; Li et al., 2019 b). Moreover, not only does As disturb the species composition of the gut microbiome but also deeply alters many important bacterial functional pathways (Chi et al., 2017 a). The size and intensity of changes are sex-specific (Chi et al., 2016). Studies by Breton et al. (2013 b) involving mice demonstrated that intestines are poor accumulators for Cd and Pb; however, changes in the gene expression of specific intestinal markers showed that these metals stimulated the epithelial inflammation in the duodenum, ileum and colon. They also found that Cd had a genotoxic effect both in the upper and the lower part of the gastrointestinal tract. Based on studies involving C57BL/6 mice it was discovered that exposure to Pb disturbs the development of the gut microbiome, the key metabolites and metabolic pathways. The performed 16S rRNA sequencing revealed that exposure to Pb altered the gut microbiome's trajectory and phylogenetic diversity, and metagenomic sequencing and metabolomic profiling demonstrated that certain metabolic pathways (e.g., of vitamin E, bile acids, energy transformations, and oxidative stress) were considerably disturbed by exposure to Pb, which can have a significant effect on the toxicity of this metal in the body (Gao et al., 2017). Other study involving mice implied a possibility of reducing the toxicity of Pb through modulation of the gut microbiota, as the administration of *Faecalibacterium prausnitzii* and *Oscillibacter ruminantium* increased the rate of production of short-chain fatty acids by the microbiota of the large intestine (Zhai et al., 2020). Pb can damage the intestinal barrier and enhance the permeability of guts, so inflammatory cytokines, agents affecting the immune system, as well as microbial metabolites such as bile acids and short-chain fatty acids, easily penetrate into the hepatic

portal vein and ultimately lead to numerous changes in the body functions (Liu et al., 2021 a). Perinatal exposure of mice to Pb decreased aerobes and increased anaerobes compared to the control group (Wu et al., 2016). Mercury (Hg) is a toxic metal that can be microbiologically converted into bioaccumulative methylmercury (MeHg), which results in a potentially toxic load on the body, as study involving adult CD-1 mice found dysbiosis of the gut microbiome after Hg exposure (Nielsen et al., 2018). The 16S rRNA sequencing for tracing changes in the gut microbiota composition of rats exposed to As, Cd, cobalt (Co), Cr or nickel (Ni) for five days showed significant alterations to the microbiota composition, whereas the response to As, Cd and Ni was observed to be dependent on the dose (Richardson et al., 2018).

In Table 7 are presented selected toxic heavy metals influencing the microbiome composition of monogastric animals.

Table 7. Influence of selected toxic heavy metals on the microbiome composition of monogastric animals

The nutritional factor	Experimental factor	Effects on gut microbiome	Target site	Animal species	References
1	2	3	4	5	6
Arsenic	As 3 mg/l, Fe 5 mg/l and 3 As mg/l + Fe 5 mg/l for 90 days	↑ *Firmicutes,* ↑ *Proteobacteria*, ↓ *Bacteroidetes*	Feces	Mice	Guo et al. (2014)
Arsenic	10 ppb or 250 ppb of sodium arsenite ($NaAsO_2$) for periods of 2, 5 and 10 weeks	↑ *Bacteroidetes*, ↓ *Firmicutes*	Colon	Mice	Dheer et al. (2015)
Arsenic	Sodium arsenite ($NaAsO_2$) (10 ppm) in drinking water for 4 weeks	↓ class *Clostridia* (in the phylum *Firmicutes)*	Feces	Mice	Lu et al. (2014)
Cadmium	Cd (20 or 100 ppm) or Pb (100 or 500 ppm) for 8 weeks	↑ *Lachnospiraceae abundance*	Feces, Cecum	Mice	Breton et al. (2013 c)
Cadmium	20 and 100 mg/kg cadmium chloride respectively for 3 weeks	↓ *Bacteroidetes,* ↓ *Lactobacillus*, ↓ *Bifidobacterium*	Feces	Mice	Liu et al. (2014)
Cadmium	100 mg/l Cd + low dietary fiber diet; Cd+ 10% IDF: 100 mg/l Cd + native wheat bran at 100 g/kg diet	↑ *Verrucomicrobia*	Feces	Mice	Li et al. (2016)
Cadmium, arsenic, cobalt, chromium, nickel	Sodium arsenite ($NaAsO_2$ – 15, 22, or 31 mg/kg/day); cadmium chloride ($CdCl_2$ – 35, 54, or 85 mg/kg/day); sodium dichromate ($Na_2Cr_2O_7$ – 44, 62, or 88 mg/kg/day); cobalt chloride ($CoCl_2$ – 27, 47, or 82 mg/kg/day); nickel chloride ($NiCl_2$ – 177, 232, or 300 mg/kg/day) for 5 days	↑ *Proteobacteria,* ↓ *Firmicutes,* ↓ *Bacteroidetes*	Feces	Rats	Richardson et al. (2018)
Chromium	Cr-enriched *Bacillus subtilis* (CEBS): basic diet+clean water (Cr 0.06 µg/ml); basic diet + water + CEBS (0.30 µg Cr/ml, 10^7 CFU/ml *B. subtilis*); basic diet + water + 1.537 µg/ml $CrCl_3 \cdot 6H_2O$ (0.30 µg Cr/ml); basic diet + water + 10^7 CFU (10^7/ml *B. subtilis*)	↓ *E. coli,* ↓ *Staphylococcus* (CEBS or normal *B. subtilis*); ↑ *Lactobacillus,* ↑ *Bifidobacterium* (CEBS and normal *B. subtilis*)	Cecum	Mice	Yang et al. (2016)
Mercury	80 mg/L $HgCl_2$ in drinking water for 90 days	↑ *Coprococcus,* ↑ *Oscillospira,* ↑ *Helicobacter,* ↓ *Ignatzschineria*, ↓ *Salinicoccus*, ↓ *Bacillus*	Cecum, rectum	Mice	Zhao et al. (2020)
Mercury	Methylmercury (4 mg/kg body weight by 28 days; 29th day – methylmercury-poisoned + sodium selenite (Na_2SeO_3) (2.74 mg/kg body weight sodium selenite)	↓ *Bacteroidetes,* ↑ *Firmicutes* in group methylmercury compared with the control group; ↑ *Bacteroidetes*, ↓ *Firmicutes* in group methylmercury+sodium selenite compared with the methylmercury group	Feces	Rats	Liu et al. (2019 b)
Mercury	Mercury sulfide (HgS) (α-HgS, 30 mg/kg), Zuotai (β-HgS, 30 mg/kg), $HgCl_2$ (33.6 mg/kg, equivalent Hg as HgS), or methylmercury (MeHg) (3.1 mg/kg, 1/10 Hg as HgS) for 7 days	the 10 phyla HgS: ↑ *Rikenellaceae*, ↑ *Lactobacillaceae*, ↑ *Helicobacteraceae*, ↓ *Prevotellaceae* $HgCl_2$: ↑ *Odoribacteraceae*, ↑ Porphyromonadaceae, ↓ *Lactobacillacea*e the 79 families HgS: ↑ *Rikenellaceae,* ↑ *Lactobacillaceae*, ↑ *Helicobacteraceae*, ↓ *Prevotellaceae* $HgCl_2$: ↑ *Odoribacteraceae*, ↑ *Porphyromonadaceae*, ↓ *Lactobacillaceae*	Duodenum, ileum	Mice	Zhang et al. (2019)

Table 7 – contd.

1	2	3	4	5	6
Mercury	Mercuric chloride ($HgCl_2$, 250 ppm, drinking water) after 30, 60, and 90 days of exposure	On day 30: ↑ *Proteobacteria*, ↑ *Tenericutes* On day 60: ↑ *Tenericutes*	Cecum	Chicken broilers	Zhou et al. (2020)
Mercury	Hg 2 mg/kg body weight ($HgCl_2$); Cu + Hg (Cu 2.5 mg/kg body weight, Hg 1 mg/kg body weight)	↓ *Sporosarcina*, ↓ *Jeotgailcoccus*, ↑ *Staphylococcus* in the group with Hg and Cu+Hg ↑ *Anaeroplasma* in the group with Cu+Hg	Cecum	Mice	Ruan et al. (2019)
Nickel	300, 600 and 900 mg/kg $NiCl_2$ for 42 days	300 to 900 mg/kg: ↓ *Bifidobacterium* spp., ↓ *Lactobacillus*, ↑ *Escherichia coli,* ↑ *Enterococcus* spp.	Ileum, cecum	Broilers chicks	Wu et al. (2014)
Nickel	Drinking water containing 400 μM $NiSO_4 \cdot 6H_2O$, for 21 days	↑ *Bacteroides*, ↑ *Intestinimonas,* ↓ *Lachnospiraceae_NK4A136,* ↓ *Lachnospiraceae_UCG-001* ↓ *Firmicutes/Bacteroides*	Cecum	Mice	Zhou et al. (2019)
Lead	0.2 ml Pb solution at 20, 100, 500, or 1000 mg Pb/kg body weight for 3 days	↓ *Coprococcus*, ↓ *Oscillospira*, ↑ *Lactobacillus* in linear manner with the Pb exposure dose.	Feces, colon	Mice	Yu et al. (2021)
Lead	$PbCl_2$ (1.34 g L^{-1} in drinking water) and/or chlorogenic acid (30 mg per kg mouse per day) for 8 weeks	↑ *Helicobacter*, ↓ *Lachnospiraceae* (Pb + chlorogenic acid)	Cecum	Mice	Cheng et al. (2019)
Lead	Chronic Pb exposure (50 ppm and 1000 ppm)	50 ppm Pb: ↓ *Ruminococcus,* ↓ *Faecalibacterium,* ↑ *Bacteroides* 1000 ppm Pb: ↓ *Faecalibacteriu*m,↑ *Bacteroides*	Cecum	Japanese quails	Kou et al. (2019)
Lead, cadmium	Cd – $CdCl_2$ or Pb – $PbCl_2$ (5, 20 and 100 ppm) for 8 weeks	↑ *Lachnospiraceae*	Feces	Mice	Breton et al. (2013 c)

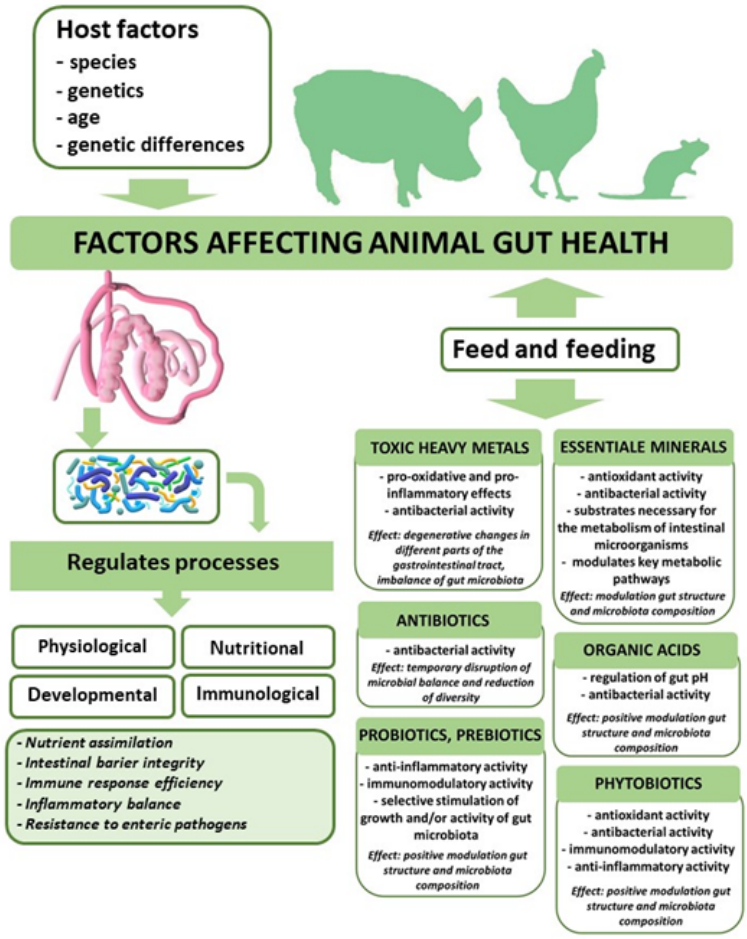


Figure 1. Factors affecting animal gut health

Summary and perspectives

A major condition for the optimum gut health is the correct function of the gastrointestinal tract, morphological integrity of intestinal epithelium, proper and effective immune response to an inflammation, as well as proper population size and composition of the microbiota, all of which, as shown in this review, can be modulated by numerous different bioactive nutritional compounds provided via intestinal tract (Figure 1). Appreciating the effect of gut microbiota and intestine structure on health parameters of the animal is a key to accomplishing good performance. Therefore, two major challenges to animal feed producers are: (1) determining the optimum microbiota for the animals' health and performance in commercial conditions, that is, discovering the microbiota that maximises the benefits and minimises the costs; and (2) designing dietary and other interventions to establish such microbiota. In many cases, well-designed *in vivo* and *in vitro* experiments, using appropriate experimental models (both livestock animals and animal models), are still required. We hope that this review may yield insights into potential bioactive nutritional compounds which may be used for manipulation of the microbiome composition and improving the morphology of the intestine of the animal. Also, new types of compounds may be used as future disease prevention and performance optimization strategies.

Conflict of Interests Statement

The authors declare that they have no conflict of interests regarding the publication of this article.

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Received: 2 V 2022
Accepted: 15 VII 2022