Review Article

Opportunities of prebiotics for the intestinal health of monogastric animals

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ABSTRACT

The goal of prebiotic applications from different sources is to improve the gut ecosystem where the host and microbiota can benefit from prebiotics. It has already been recognized that prebiotics have potential roles in the gut ecosystem because gut microbiota ferment complex dietary macronutrients and carry out a broad range of functions in the host body, such as the production of nutrients and vitamins, protection against pathogens, and maintenance of immune system balance. The gut ecosystem is very crucial and can be affected by numerous factors consisting of dietary constituents and commensal bacteria. This review focuses on recent scientific evidence, confirming a beneficial effect of prebiotics on animal health, particularly in terms of protection against pathogenic bacteria and increasing the number of beneficial bacteria that may improve epithelial cell barrier functions. It has also been reviewed that modification of the gut ecosystem through the utilization of prebiotics significantly affects the intestinal health of animals. However, the identification and characterization of novel potential prebiotics remain a topical issue and elucidation of the metagenomics relationship between gut microbiota alteration and prebiotic substances is necessary for future prebiotic studies.

1. Introduction

The gastrointestinal tract (GIT) has long been known as a harbor of gut microbiota. The healthy relationship between gut microbiota and animal is important for the GIT. The mammalian GIT microbiota comprises approximately 10^{14} microorganisms and includes a wide diversity of microbial species (Míguez et al., 2016; Yang and Xu, 2018). The GIT is the most heavily colonized organ and comprises various sections with different environmental conditions and microbial profiles. The microbiota in the GIT is associated with a broad range of functions within the host, including the fermentation of complex macronutrients, nutrient and vitamin production, cellulose fermentation, protection from pathogens, maintenance of the balance of the immune system, and physiological metabolism in distal organs or tissues (Han et al., 2018; Li et al., 2020; Yin et al., 2018, 2020).

Within the GIT, the microbes must adapt to the limitations imposed by the environment found along the tract. These include the biochemical pathways available to them, such as those imposed by anaerobicity. Fermentation and sulfate reduction of dietary and host carbohydrates can supply energy in the gastrointestinal ecosystem (Thursby and Juge, 2017). Growth, development, and physiologic homeostasis of the gut is intricately related to microbial interaction with the gut mucosa and with indirect "cross-talk" between the host and microbial metabolites. Various animal

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studies have indicated the crucial contributions of the gut microbiota in the producing of short-chain fatty acids (SCFA) in the colonocytes, which play a crucial role in the regulation of the gene expression in colonocytes that are related to some anti-inflammation, maintenance of the gut barrier function, water-electrolyte balance, and several effects on intestinal metabolism (Cheng et al., 2018; Pan et al., 2019). In addition, the gut microbiota is involved in the production of different kinds of antibacterial peptides, such as bacteriocins, and the regulation of intestinal mucin production by goblet cells (Wrzosek et al., 2013), which further regulate bacterial adhesion to epithelial cells (Ye et al., 2015).

Recent studies have indicated that a diet has a considerable effect on microbiota modulation and is now regarded as a serious approach to regulate microbiota dysbiosis (Donaldson et al., 2016; Lalles, 2016). Meta-transcriptomic studies showed that the microbiota in the ileum is driven by the capacity of the microbial members to metabolize simple carbohydrates, reflecting the adaptation of the microbiota to the availability of nutrients in the small intestine (Zoetendal et al., 2012). Moreover, some microorganisms in the GIT provide the enzymes and biochemical pathways that are needed to digest the complex nondigestible carbohydrates and protein. In addition, microbiota metabolism is a key factor for the synthesis of vitamin K, absorption of calcium, magnesium and iron, and the biotransformation of bile acids. Short-chain fatty acids are generated after the fermentation cycle, which provide energy for colonocytes. Also, SCFA can stimulate proliferation and differentiation of intestinal epithelial cells in vivo, induction of mucin secretion, and antimicrobial peptide production (Chang and Lin, 2016; Wang et al., 2017). Therefore, the modulation of gut microbiota has become a prominent technique to improve host health, protect against infection and diseases, and produce important vitamins and energy, the latter of which can play a crucial role in physiological regulatory networks. Over the past decades, different nutritional strategies, prebiotics, probiotics, antimicrobial agents, and fecal microbiota transplantation have shown significant potential for shaping the gut microbiota in humans and animals (Azad et al., 2018a, 2018b; Claesson et al., 2012; Ji et al., 2018; Tachon et al., 2013).

In this regard, the outcomes of various studies indicated that dietary prebiotics have the potential to modulate intestinal health infections by altering the gut microbiota population (Gibson et al., 2017; Pham et al., 2018). This review focuses on recent studies of prebiotics and their effects on gut health, particularly in relation to nutrient digestibility and absorption, and immunomodulation.

2. Prebiotics and their mechanisms of action

The term "prebiotic" is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon, and thus improves host health" (Gibson and Roberfroid, 1995). However, only a few carbohydrate compounds have been considered prebiotics, including fructo-oligosaccharides (FOS), inulin, galacto-oligosaccharides (GOS), and lactulose, which play a role in the enrichment of native *Lactobacillus* spp. and/or *Bifidobacterium* spp. At the sixth meeting of the ISAPP (International Scientific Association of Probiotics and Prebiotics) in 2008, the definition of "prebiotics" was updated as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon the host health" (Gibson et al., 2010). Recent advanced research techniques for the microbiome (e.g.,

high-throughput sequencing) have enhanced the knowledge of the microbiota composition and aided in the identification of other substances influencing colonization. However, this understanding of the wide range of beneficial microorganisms is affected by prebiotics and is also effective for extraintestinal sites directly or indirectly (Collins and Reid, 2016). Moreover, prebiotics as a diet supplement have extended to production and companion animal food and categories beyond food. In addition, prebiotics may affect the gut microenvironment and the utilization of other undigested dietary ingredients and compounds, such as antibiotics, minerals, and vitamins. Therefore, the definition has been updated to "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson et al., 2017). By using high-throughput sequencing technologies, recent studies confirmed the selectivity of prebiotic fermentation on gut microbial ecology. These research studies revealed that bifidobacteria not only selectively responded to specific prebiotic compounds but also modulated other groups of bacteria, including *Faecalibacterium prausnitzii* in one trial, and increased *Anaerostipes* spp., decreased *Bilophila* spp. in another trial (Dewulf et al., 2013; Vandeputte et al., 2017). Therefore, the above-mentioned results indicate that prebiotics can modulate the beneficial gut microbiota and thus impact on host health.

Mechanistically, prebiotics are not digested in the upper GIT and they are thought to be fermented by selective residential bacteria once they reach the colon. The environment in the colon is suitable for fermentation and commensal growth due to its slow transit time, nutrient availability, and pH. The fermentation of carbohydrates in the colon leads to the production of SCFA, mainly acetate, propionate, butyrate, and other metabolites, such as lactate, pyruvate, ethanol, and succinate (Janssen and Kersten, 2015; Sarbini and Rastall, 2011; Slavin, 2013). Fermentation end-products, such as butyrate, can act as an energy source for colonocytes, even when competing substrates (e.g., glucose and glutamine) are available (Zambell et al., 2003). Furthermore, the growth of pathogenic organisms can be inhibited by the production of SCFA. In addition, SCFA production can lower the luminal pH and thus inhibits peptide degradation and the resultant formation of toxic compounds, such as ammonia, amines, and phenolic compounds, and suppresses the activity of undesirable bacterial enzymes (Cummings and Macfarlane, 1991; Jarrett and Ashworth, 2018; Slavin, 2013). On the other hand, the presence of prebiotics such as oligosaccharides in the intestine could also increase the residence probiotic strains by bacterial adhesion properties. Prebiotics have also been found to act as decoy receptors to inhibit the adhesion of some pathogenic bacteria to the intestine as reviewed by Hickey (2012). Furthermore, the butyrate-producing strains in Firmicutes families Lanchnospiraceae and Ruminococcaceae were shown different growth profiles in the presence of FOS, GOS, and xylo-oligosaccharides (XOS) (Rawi et al., 2020; Scott et al., 2020). Moreover, colonic fermentation can modulate the gut microbial population, such as the increase in bifidobacteria and lactobacilli in the GIT. In addition, prebiotics have been shown to decrease the number of *Bacteroides*, proteolytic clostridia, and *Escherichia coli* (Parnell and Reimer, 2012; Zhang et al., 2015). However, fermentation in the colon and modulation of the gut microbiota are important mechanisms of action for prebiotics. Indeed, prebiotics such as oligosaccharides have also been shown to increase the integrity of intestinal mucosa by enhancing villus height and the release of mucin and mucosal biofilm composition (Wan et al., 2018a; Yasmin et al., 2015). Therefore, a number of factors influence gut microbiota modulation, which can also affect the host physiological conditions and the intestinal health of the host.

3. Prebiotics and intestinal health of monogastric animals

The term "intestinal health" is attracting significant interest among veterinarians, nutritionists, and researchers over the past few years (Celi et al., 2019; Kogut and Arsenault, 2016). This interest arises from the desire to improve gastrointestinal health aimed at animal production, such as growth, survival, and yield (milk, meat and egg quality). However, it is difficult to define "intestinal health". Celi et al. (2017) recently proposed 6 major domains that may integrate the functionality of intestinal health. The proposed domains include diet, digestion and absorption, normal and stable gut microbiota, effective immune status, gut mucosa, and neurosecretion and motor function of the gut. And, all of these may play a crucial role in gastrointestinal physiology, animal health, welfare, and performance. The use of prebiotics has become a topic of great interest because it is thought to have beneficial effects on intestinal health. If these claims for prebiotics are verified, they would be very important tools in pig production, especially as a feed additive.

The GIT of the monogastric animal plays a crucial role in nutrient digestion and absorption, and maintains the barrier function against malignant pathogens and antigens. Therefore, it is necessary to maintain intestinal functions because malfunction of the intestine is directly related to animal health and growth (Lee and Kim, 2018; Wijtten et al., 2011). In pig production, malfunction of the intestine can contribute to intestinal and immune dysfunctions, leading a decreased growth of piglet (Guevarra et al., 2019). Once the piglet is born, the first 4 wk are the most important in developing the GIT because in this period, GIT organs are growing faster than other organs of the body (Pluske et al., 2018). These changes in the newborn piglets are linked with the local GIT blood flow, accumulation of colostral proteins, and epithelial cell turnover, which influence changes in body weight, gastrointestinal structure, and cell apoptosis (Pluske, 2011). Therefore, dietary nutrients are essential for the functional development and growth of the GIT during the early stage of life. On the other hand, weaning is the most significant event in the life of pigs. During the weaning transition, piglets experience a number of stressors, with the most important being the abrupt change in the diet from milk to dry and less digestible solid-based feed, which may significantly reduce energy intake to maintain epithelial structure, reduce transmucosal resistance, and increase the secretory activity of the small intestine. This damage to the epithelial layer may also decrease the nutrient digestibility (Kim et al., 2012). Nutrient digestibility is also a key factor in the growth performance of monogastric animals.

Modification of the gut ecosystem through the utilization of prebiotics affects the intestinal health of the host. Fructo-oligosaccharides, GOS, inulin, arabinoxylo oligosaccharides (AXOS) and XOS, chito-oligosaccharides (COS), isomalto-oligosaccharides (IMO), and dietary carbohydrates are among the most studied prebiotics in humans and animals. Table 1 presents the most significant recent results of various studies on the influence of prebiotics on intestinal health. Other less common potential prebiotics, including mannan-oligosaccharides (MOS), inulin, glucomannan oligosaccharides (GMO), alginate oligosaccharides (AOS), and pectin oligosaccharides (POS), have also been extensively studied as prebiotics in human and animal health improvement (Table 2).

Inulin, FOS, GOS, transgalacto-oligosaccharides, and lactulose are the main prebiotics that have been extensively studied in animal health promotion as feed additives because these prebiotics are easily fermented in the colon and will therefore result in decreased luminal pH and increased SCFA production (Bach Knudsen et al., 2012; Li et al., 2018). Increased SCFA can reduce the fermentation of proteins in the intestinal tract. Short-chain fatty acids products, such as butyrate, regulate cell growth and induce differentiation and apoptosis in the small intestine, resulting in improved cell proliferation and digestion and absorption capacities of the small intestine (Linberg, 2014; van der Aar et al., 2017). A recent study with different concentrations of inulin supplementation (low concentrations: 0.5, 1, 1.5, and 2 g/d and high concentrations: 0.75, 1.5, 2.25 and 3 g/d for wk 1, 2, 3 and 4, respectively) in newborn piglets revealed that inulin supplementation increased growth performance during the suckling period. Furthermore, lower concentrations of inulin increased the jejunal and ileal villus height compared to higher concentrations during weaning and postweaning. Short-chain fatty acids production also increased after the addition of inulin during weaning (Li et al., 2018). Supplementation of FOS (5 g/d) to newborns (2 to 14 d of age) showed increased body weight gain but did not change the intestinal structure compared with the respective controls (Schokker et al., 2018).

Increased villus height and villus height-to-crypt depth ratio are associated with digestion and absorption of nutritious substances that are related to growth performance. Growth factors, such as the glucagon-like peptide 1 (GLP-1), GLP-2, epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), and IGF-1 receptor (IGF-1R) proteins, are also able to increase the proliferation, differentiation, and apoptosis of intestinal epithelial cells (Deng et al., 2016; Shawe-Taylor et al., 2017; Wang et al., 2020). For example, oral administration of 10-mL GOS in solution (1 g/kg BW) to suckling piglets upregulated the mRNA expression of *IGF-1, IGF-1R, EGF, GLP-1*, and *GLP-2*. In addition, dietary GOS administration increased the small intestinal length (Tian et al., 2018).

As previously mentioned, weaning is the most important event in monogastric animals. A large body of evidence has revealed that prebiotic supplementation can maintain gastrointestinal functionality. For example, dietary supplementation of COS at 150 mg/kg in weaned piglets enhanced growth performance, the nutrient digestibility of crude protein, fat, and calcium, crypt cell proliferation, and intestinal morphology (Suthongsa et al., 2017; Thongsong et al., 2018). The addition of IMO supplementation at 6 g/kg for weanling pigs improved growth performance and increased apparent total digestibility of dry matter, organic matter, and gross energy. The ileum villus height and SCFA concentration in the cecum and colon also increased with IMO dietary supplementation (Wang et al., 2016; Wang et al., 2016; Wu et al., 2017). Interestingly, maternal prebiotic supplementation can also affect the gastrointestinal development of offspring by transferring effective metabolites through the placenta. Duan et al. (2016) supplemented dietary MOS from late gestation (d 86 of gestation) until weaning. Pregnant sows were fed MOS (400 mg/kg), and their offspring (from 7 to 28 d of age) received MOS (800 mg/kg). Maternal prebiotic supplementation increased the average daily weight gain during lactation. In another study, maternal dietary short-chain FOS (scFOS) supplementation increased SCFA production, particularly acetate, propionate, valerate, and caproate, in suckling piglets (Le Bourgot et al., 2017).

Moreover, prebiotics have been shown to be suitable for enrichment of the bioavailability of minerals. Minerals such as trace metals, iron, calcium, copper, and zinc are essential for the host organism function (Whisner and Castillo, 2018). Inulin supplementation (1%, 2%, and 3% of standard inulin) to pigs increased plasma zinc and iron concentrations (Samolinska and Grela, 2017). Moreover, higher concentrations of XOS (between 0.1 and 0.5 g/kg) have been shown to improve bone mineralization by decreasing the rate of carbonate substitution for phosphate (S Wang et al., 2017).

Table 1
Commonly used prebiotics for intestinal health.

Prebiotics	Subjects	Dosage	Duration	Outcomes	References
FOS	Methionine-choline deficient C57BL/6J mice	5%	3 wk	↑ Villus height, small intestine length, ZO-1, SCFA ↑ *Lactobacillus* spp. ↓ *Clostridium* spp.	Matsumoto et al. (2017)
FOS	7-wk-old male C57BL/6J mice	5% and 25%	4 wk	↑ *Bifidobacterium, Coprococcus, Enterococcus,* and *Blautia,* ↓ Firmicutes ↑ SCFA production	Mao et al. (2018)
FOS	3-wk-old male Sprague–Dawley rats	10%	2 wk	↑ Cecum *Bifidobacterium* ↓ Cecum *Lactobacillus* ↑ Propionate, n-butyrate and total SCFA	Yamaguchi et al. (2018)
FOS	10-wk-old C57BL/6J mice	0.3 g/mouse	8 wk	↑ Expression of intectin, regenerating islet-derived protein 3-gamma ↓ Firmicutes-to-Bacteroidetes ratio, *Lactobacillus, Coprococcus, Eubacterium, Allobaculum, Turicibacter*	Everard et al. (2014)
FOS	3-wk-old female C57BL/6J mice	8 g/kg BW	2 wk	↑ Intestinal expression of IL-23, IL-1β, mucosal mast cell, SCFA production	Chen et al. (2017)
FOS	*Salmonella* challenged laying hens	0.5% and 1.0%	3 wk	↑ IL-1β, IL-18, and IFN-γ ↓ *Salmonella*	Adhikari et al. (2018)
FOS	Dogs	1.5 g/kg	4 wk	↑ Bifidobacteria, acetic-to-propionic acid ratio ↓ pH in faces, acetic + n-butyric acid-to-propionic acid ratio	Pinna et al. (2018)
FOS	Weaned piglets	0.6%	7 d	↑ Bifidobacteria, *Lactobacillus* in jejunum ↑ IFN-γ ↓ Proteobacteria in jejunum and ileum ↓ IL-4, IL-10	Chang et al. (2018)
scFOS	18-wk-old obese male C57BL/6J mice	10%	4 wk	↑ Cecal and colonic crypt depth, transmural resistance ↑ Actinobacteria, Verrucomirobia	Liu et al. (2016)
scFOS	Humanized Gnotobiotic diet induced obese mice	10%	7 wk	↑ Bifidobacteria ↑ Full cecum weight, empty cecum weight ↓ *Clostridium* spp.	Respondek et al. (2013)
scFOS	Adult pigs and offspring piglets	Adult pigs (10 g/d), weaning piglets (0.15%)	4 wk	↑ Bacteroidetes, *Prevotella, Bacteroidales,* Ruminococcaceae ↓ Firmicutes ↑ Total concentration of SCFA	Le Bourgot et al. (2018)
GOS	Humans	0 to 10 g/d	16 wk	↑ Actinobacteria, bifidobacteria, Firmicutes	Davis et al. (2011)
FOS, GOS	Humans	16 g/d	2 wk	↑ *Bifidobacterium* ↓ *Ruminococcus, Phascolarctobacterium, Coprococcus, Oscillopira, Salmonella, Enterobacter*	Liu et al. (2017)
α-GOS	Fifty-six-wk old male CD-1 (ICR) IGS mice	0.083, 0.42, and 0.83 g/(kg·d)	6 wk	↑Bifidobacteria, lactobacilli, *Clostridium leptum* ↑ SCFA	Dai et al. (2017)
GOS	4-wk-old male Wister rat	1%	2 wk	↑ Bifidobacteria in large intestine, *Bifidobacterium animalis, Eubacterium rectale/Clostridium coccoides* in cecum and colon ↓ *C. leptum* in cecum	Marin-Manzano et al. (2013)
GOS	SPF mice	1%	2 wk	↑ *Bifidobacterium, Lactobacillus, Bacteroides,* Clostridiales ↓ *Bacteroidales, Helicobacter, Clostridium*	Monteagudo-Mera et al. (2016)
scGOS	Humans	1.5 to 15 g/d	36 d	↑ *Bifidobacterium, Faecalibacterium, Lactobacillus*	Azcarate-Peril et al. (2017)
GOS	Suckling piglets	1 g/kg BW	3 wk	↑ intestinal length, ZO-1, TGF-β, GLP-2 ↓ Crypt depth in jejunum, IL-12	Tian et al. (2018)
High-purity GOS	In vitro and in vivo	1%	5 wk	↑ *Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus casei*	Hong et al. (2016)
scGOS/lcFOS	*IL-1Ra* deficient mice	1% to 5% (90% scGOS and 10% lcFOS)	8 to 10 wk	↑ Lachnospiraceae and *Lactobacillus* ↓ *Enterococcus* and *Clostridium*	Rogier et al. (2019)
COS	Weaned piglets	100 mg/kg		↑ *Bifidobacterium* ↑ Villus height, tight junction protein, IL-6, TNF-α ↓ *Escherichia coli*	Wan et al. (2017)
COS	Weaned piglets	30 mg/kg	2 wk	↑ Intraepithelial lymphocytes number, goblet cells, IL-10, secretory immunoglobulin, ZO-1 ↓ Villus height, villus height-to-crypt depth ratio	Xiong et al. (2015)
COS	*E. coli K88*⁺ challenged piglets	400 mg/kg	2 wk	↑ Villus height, villus height-to-crypt depth ratio ↓ Crypt depth	Aluko et al. (2017)
COS	ICR male mice	1 to 100 mg/(kg·d)	2 wk	↑ Colon length, epithelial architecture ↓ Mucosal injury, TNF-α, IL-6	Yousef et al. (2012)
COS	Wild-type male C57BL/6J mice	200 mg/(kg·d)	3 mo	↑ *Akkermansia,* Lachnospiraceae ↓ *Helicobacter, Ruminococcus,* Lachnospiraceae NK4A136, *Odoribacter* ↑ Tight junction ZO-1, ↓ TNF-α, MCP-1 (a macrophage biomarker)	Zheng et al. (2018b)
AOX and inulin	In vitro	5 g/L	48 h	↑ *Bifidobacterium, Bacteroides, Prevotella* ↑ Acetate, propionate, butyrate, IL-6, IL-10 ↓ Colonic pH	Van den Abbeele et al. (2018)
AOX, XOS	In vitro	5 g/L	48 h	↑ *Bifidobacterium adolescentis, Lactobacillus brevis* ↓ pH	Mathew et al. (2018)
XOS	Humans	1.2 g/d	6 wk	↑ *Lactobacillus* spp., *Bifidobacterium* spp. ↓ *Clostridium perfringens*	Lin et al. (2016)
XOS	Pigs	200 mg/kg	4 wk	↑ Villus height-to-crypt ratio ↑ Lactobacilli ↓ *E. coli*	Liu et al. (2018)

Table 1 (*continued*)

Prebiotics	Subjects	Dosage	Duration	Outcomes	References
XOS	Pigs	100 to 500 g/t	70 d	↓ Proteobacteria, *Citrobacter* ↑ Firmicutes, *Lactobacillus*, SCFA	Pan et al. (2019)
XOS	Weaned piglets	0.01%	Weaned	↑ *Streptococcus, Turicibacter*, ZO-1 ↓ *Lactobacillus*, IFN-γ	Yin et al. (2019)
XOS	Laying hens	0 to 0.05%	8 wk	↑ Villus height, villus height-to-crypt depth ratio, SCFA, TNF- α, IL-2 ↑ Bifidobacteria	Ding et al. (2018)
XOS, MOS	Arbor Acres male broiler chickens	XOS at 2 g/kg, MOS at 1 g/kg	5 d	↑ *Coprococcus, Ruminococcus, Enterococcus, Clostridium, Lactobacillus, Roseburia* ↑ TNF-α ↓ *Salmonella*	Pourabedin et al. (2017)

FOS = fructo-oligosaccharides; ZO = zonula occludens; SCFA = short-chain fatty acids; IFN = interferon; scFOS = short-chain FOS; GOS = galacto-oligosaccharides; TGF-β = transforming growth factor-β; scGOS = short-chain GOS; GLP-2 = glucagon-like peptide-2 lcFOS = long-chain FOS; COS = chito-oligosaccharides; MCP = monocyte chemoattractant protein-1; TNF = tumor necrosis factor; IL = interleukin; AOS = alginate oligosaccharides; XOS = xylo-oligosaccharides; MOS = mannan-oligosaccharides. "↑" and "↓" mean respectively "increased" and "decreased" after prebiotic supplementation.

Table 2
Other less common potential prebiotics for intestinal health.

Prebiotics	Subjects	Dosage	Duration	Outcomes	References
AOS	Pigs	100 mg/kg	2 wk	↑ Villus height, villus height-to-crypt depth ratio, goblet cells	Wan et al. (2018b)
AOS	Pigs	100 mg/kg	2 wk	↑ Intestinal occludin, intestinal catalase activity ↓ TNF-α, IL-1β	Wan et al. (2018a)
MOS	Wister rats	1 mg/kg	1 mo	↑ Villus height ↓ IL-10, IFN-γ, IL-1β	Levi et al. (2018)
MOS	Laying hens	0 to 2 g/kg	11 wk	↑ Ileal nutrition digestibility ↓ *Salmonella, E. coli*	Ghasemian and Jahanian (2016)
Konjac MOS	Mice C57BL/6J	2 to 8 g/(kg·d)	5 wk	↑ *Bifidobacterium, Akkermansia* ↓ *Allobaculum* spp.	Zheng et al. (2018a)
GMO and inulin	Wistar rats	—	2 wk	↑ Bifidobacteria, lactobacilli ↑ Acetic, propionic, butyric, and total SCFA in cecal content ↓ *E. coli* ↓ Cecal pH	Harmayani et al. (2014)
MOS	Broilers	0.2% or 0.5%	38 d	↑ Bifidobacteria, *Lactobacillus* ↑ Villus height, goblet cells ↓ *E. coli, Campylobacter*	Baurhoo et al. (2009)
MOS	*Salmonella* challenged broilers	0.1% to 0.3%	24 d	↑ Villus height, villus height-to-crypt depth ratio, villus surface area	Rajani et al. (2016)
Konjac oligosaccharides	Mice	0.5 to 2 g/kg BW	35 d	↑ Bifiodobacteria, lactobacilli ↑ Acetic acid, butyric acid, total SCFA, IL-10	Zeng et al. (2018)
Inulin	Pigs	1.5%	110 d	↑ Bacteroidetes, Proteobacteria, Verrucomirobia, Actinobacteria, Fibrobacteres ↑ SCFA ↓ Firmicutes, Tenericutes, Letisphaerae	Zhou et al. (2017)
Inulin	Pigs	3%	d 21 gestation to d 14 lactation	↑ *Enterococci* ↓ *Ecobacteria*, lactobacilli, *L. reuteri, L. amylovorus, L. johnonii, L. mucosae, C. leptum, C. coccoides* ↑ Total SCFA ↓ Fecal pH	Passlack et al. (2015)
Inulin	Arbor Acres SPE chickens	2.5 to 20 g/kg	3 wk	↑ Acetate, propionate, villi height, mucin-2, claudin-1 ↓ IL-6, crypt depth	Song et al. (2018)
Pectin	Dynamic gastrointestinal stimulator model	30 g/L	14 d	↑ *Bifidobacterium* spp., *Bacteroides* spp., *Faecalobacterium prausnitzii* ↑ SCFA ↓ *Lactobacillus* spp.	Ferreira-Lazarte et al. (2019)
POS, AX	Wister rats	3%	7 wk	↑ Acetate, propionate, butyrate, total SCFA ↑ *Lactobacillus*, Lachnospiraceae ↓ Bacteroidetes	Tian et al. (2016)
IMO	Pigs	6 g/kg	4 wk	↑ Streptococcaceae, *Collinsella* ↑ Villus height, volatile fatty acids	Wu et al. (2017)
IMO	Swiss albino mice	1 g/kg BW	12 wk	↑ *Lactobacillus* spp., bifidobacteria, *Akkermansia muciniphila, Roseburia* spp. ↑ TNF-α, IL-1β, SCFA, goblet cells, villus height, ZO-1 ↓ IL-6, GLP-1	Singh et al. (2017)
Resistant potato starch	Weaned piglets	5%	12 d	↑ *Terriporobacter, Sarcina, Clostridium sensu stricto 1*, butyrate, and lactate	Trachsel et al. (2019)
Saccharomyces-derived prebiotics	Broiler chickens	50 and 100 g/t	6 wk	↓ *Camphylobacter*	Froebel et al. (2019)

AOS = alginate oligosaccharides; TNF = tumor necrosis factor; IL = interleukin; MOS = mannan-oligosaccharides; GMO = glucomannan oligosaccharides; SCFA = short-chain fatty acids; POS = pectin oligosaccharides; AX = arabinoxylans; IMO = isomalto-oligosaccharides; ZO = zonula occludens; GLP-1 = glucagon-like peptide-1. "↑" and "↓" mean respectively "increased" and "decreased" after prebiotic supplementation.

4. Prebiotics and immunomodulation of monogastric animals

The GIT is considered the largest and most important organ of the immune system, where more than 70% of the cells of the immune system are located (Vighi et al., 2008). The relationship between the GIT and immune system is attaining increasing significance, not only in terms of health and diseases, but also in terms of intestinal functionality (Celi et al., 2017). Physiologically, the GIT plays a pivotal role as a barrier function against pathogens and antigens. The immune system of the GIT has a distinctive capability to distinguish between beneficial and potentially high-risk materials. Prebiotics can stimulate or modulate the immune system by promoting several components of the intestinal immune system. Some probiotics can modulate the immune system by binding the G protein receptors within gut-associated lymphoid tissue. Immune function can be modulated by prebiotics both directly or indirectly (Khangwal and Shukla, 2019). The primary layer of the intestinal barrier is composed of a mucus layer, which is formed by an inner layer with high concentrations of secretory immunoglobulin A (sIgA) and mucin and by an outer layer associated with the microbiota. Prebiotics are productive weapons by different methods, for example, by altering mucus production, decreasing the connection between bacteria and the epithelial barrier, improving rigid connections, increasing cell endurance, and the initiation of IgA (Bischoff et al., 2014; Celi et al., 2019). These impacts can be executed by changing tight junction proteins across the membrane and selectivity of rigid junctions (de Kivit et al., 2014). Toll-like receptors (TLR) are an ancient conserved family of pattern-recognition receptors, which play pivotal roles in the innate immune system. The intestinal gut microbiota can activate TLR4 to regulate host health by protecting against severe intestinal injury (Yiu et al., 2017). Some specific types of prebiotics, such as COS, inulin-type fructans, XOS, and AOS, have been reported to have immunomodulatory effects in monogastric animals (Ding et al., 2018; Vogt et al., 2015; Wan et al., 2018b; Xiong et al., 2015).

Another benefit of prebiotics is that they can be fermented by gut microbes to produce SCFA and other beneficial metabolites with anti-inflammatory properties. Short-chain fatty acids produced by the fermentation of prebiotics in the intestine have been found to stimulate the intestinal mucosal immune system (Bach Knudsen et al., 2018; Diao et al., 2019; Kong et al., 2014; Parada Venegas et al., 2019). The impact of dietary inulin and FOS on the immune system has been summarized in a study, which concluded that dietary inclusion had a positive impact on immune biomarkers and on gut-associated lymphoid tissues, with specific reference to cells such as Peyer's patches (Seifert and Watzl, 2007). A number of studies have investigated the immune response in monogastric animals. A recent study was carried out with dietary XOS supplementation (0.1%) in weaned pigs revealed that dietary XOS improved the intestinal barrier function by upregulating the tight junction proteins, zonula occludens-1 (ZO-1) and claudin 1, and reducing interferon (IFN)-γ compared with the control (Yin et al., 2019). The addition of IMO at differernt concentrations (0.2% to 0.8%) in weaned pig feed for 4 wk was found to increase immunoglobulins, i.e. IgA, IgM, and IgG, in serum with increasing IMO supplementation (Wang et al., 2016). A low dietary dose of COS (30 mg/kg) for 14 d significantly increased sIgA in the duodenum and ileum and changed the mRNA expression of occludin in the ileum and ZO-1 in the jejunum and ileum (Xiong et al., 2015).

Cytokines play a vital role in the modulation of the inflammatory response in the intestinal tract (Azad et al., 2018c). In the GIT, pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IFN-γ, interleukin (IL)-1β, IL-2, and IL-6, can play an important role in modulating the inflammatory response when the GIT is infected with pathogens. To increase the intestinal permeability, the endocytosis of tight junction proteins can be induced by pro-inflammatory cytokines. The upregulation of proinflammatory cytokines causes inflammation in the intestinal mucosal immune system. Anti-inflammatory cytokines, such as IL-4, IL-10, and transforming growth factor-β have the ability to control the duration and magnitude of the inflammatory response by inhibiting the production of proinflammatory cytokines (Guo et al., 2020; Han et al., 2013; Sun et al., 2015; Tang et al., 2020). A number of studies have outlined that prebiotics positively affect the functionality of the immune system by changing the expression of pro-inflammatory cytokines (Hu et al., 2018; Wan et al., 2018a; Wang et al., 2016a; Xiao et al., 2016). Furthermore, prebiotics have been shown to modulate the immune system by upregulating the anti-inflammatory cytokines (Tian et al., 2018; Xiong et al., 2015). The changing expression of cytokines impacted by prebiotics on the immune system has been reported in many investigations through their direct or indirect impact by the production of SCFA. For example, a study was carried out with maternal dietary supplementation of scFOS (0.15%) during gestation and lactation and evaluated the prebiotic effects on immunomodulation of their weaned piglets. The addition of maternal scFOS increased the expression of IFN-γ and IL-4 in the ileal mucosa, whereas it decreased ileal TNF-α. Furthermore, scFOS supplementation displayed a higher concentration of SCFA being produced. Finally, it has been concluded that SCFA production in the intestine changed cytokine profiles (Le Bourgot et al., 2017). In another study, a low dosage of COS supplementation upregulated the expression of the anti-inflammatory cytokine IL-10 but did not change the proinflammatory cytokines IL-1β and IL-2 in the intestines of weaned piglets (Xiong et al., 2015). Therefore, these investigations suggest that prebiotics can assist in the improvement of the immune system by direct or indirect approaches through the production of SCFA. However, the immune system of monogastric animals needs further research to fully understand its immunomodulatory effects.

5. Prebiotics and intestinal microbiota modulation of monogastric animals

The GIT is a prominent and robust area for microbial colonization, and maintains not only the intestinal health but also the overall health of the host. The gut microbiota of the GIT plays an important role in processing signals and cues from the environment and delivering them to the host (Celi et al., 2019; Dietert and Silbergeld, 2015). However, a number of factors influence the diversity and activity of the intestinal microbiota, such as colonization and associated succession of inhabitation, dietary composition, feeding methods, feed processing, feed additives, antimicrobial agents, disease load, season, environment, stress, and genetics (Guevarra et al., 2019; Ji et al., 2019; Rinninella et al., 2019; Ruczizka et al., 2019). Furthermore, the gut microbiota displays a compromise between supportive barrier functionality, synthesis of beneficial nutrients and proteins, and improved energy accumulation from diets, and the deleterious effects of inflammatory and clinical or subclinical pathologies (Celi et al., 2017; Pluske et al., 2018).

Microbial fermentation of prebiotics by intestinal gut bacteria in the colon leads to the production of a range of metabolites, including SCFA (primarily butyrate, acetate, and propionate), lactate, succinate, ethanol, and gases. Thus, the acidic environment in the colon can change the microbiota composition, which helps to suppress the growth of some potential pathogens such as E. coli, Clostridium, Streptococcus faecalis, and Proteus, and enhances the growth of some beneficial bacteria, including bifidobacteria, lactobacilli, and Eubacterium (Morrison and Preston, 2016; O'Callaghan and van Sinderen, 2016; Zhang et al., 2015). For

example, in a mouse colitis model, gastrointestinal inflammation occurred because of an increased population of pathogenic bacteria Enterobacteriaceae and *E. coli* and a reduction in the number of *Lactobacillus johnsonni* (Jang et al., 2018). A number of studies have revealed that dietary prebiotics can increase lactobacilli and reduce pathogenic bacteria in the GIT by changing the gut environment (Ahmadi et al., 2019; Lockyer and Stanner, 2019; Zhang et al., 2018). In addition, prebiotics have also been shown to increase some other beneficial bacteria, such as Verrucomicrobia, Erysipelotrichaceae, *Akkermansia,* and *Faecalibacterium,* and reduce pathogenic bacteria, such as *Salmonella,* Proteobacteria, and Firmicutes (Monteagudo-Mera et al., 2018; Zhang et al., 2018).

Over several years, growing evidence has shown a cross-talk between the host immune system and the intestinal microbiota. There is a large body of evidence from several species that shows the intestinal microbiota drives the improvement and function of the immune system by regulating the interaction between the host and intestinal microbiota (Brown et al., 2013; Kamada et al., 2013; Stokes, 2017). For example, certain intestinal commensal bacteria produce SCFA, which can reduce the intestinal pH to inhibit the growth of certain intestinal pathogens (Parada Venegas et al., 2019). Prebiotic supplementation has been shown in various studies to increase certain beneficial bacteria and reduce pathogenic bacteria along with the production of SCFA (Kong et al., 2014; Liu et al., 2017; Lin et al., 2016). Lipopolysaccharide is another powerful inflammatory mediator that is naturally released during the bacterial life cycle. In elevated intestinal permeability during gastrointestinal complications, the elevated lipopolysaccharide levels in fecal matter or serum were accompanied by an increase in the population of *E. coli* and a decrease in the number of lactobacilli (Adewole et al., 2016; Jang et al., 2018). Dietary supplementation of prebiotic XOS (200 mg/kg) in pigs significantly decreased the fecal *E. coli*, but increased the number of lactobacilli (Li et al., 2018). Furthermore, supplementation of prebiotic MOS in broilers (0.08% to 0.5%) has been found to potentially increase beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* and decrease harmful bacteria such as *Salmonella, E. coli, Clostridium perfringens,* and decrease potential pathogens such as *Campylobacter* (Baurhoo et al., 2009; Corrigan et al., 2015).

Enterotoxigenic *E. coli* (ETEC) is one of the main causes of diarrhea and can cause lower production performance in intestinal health. Adherence of ETEC to the epithelium colonizes the small intestine and releases enterotoxin and accounts for more gastrointestinal disorders (Aluko et al., 2017; Guan et al., 2019; Lin et al., 2016). To minimize the effects caused by ETEC, anti-microbial growth promoters are used for an extended period of time, with the aim of minimizing gastrointestinal disorders and promoting growth. However, several studies have shown that prebiotics can act as alternative sources for antimicrobial growth promoters. For example, prebiotics such as COS can bind to the anionic cell surface of Gram-negative bacteria (*E. coli)* to change the outer membrane permeability and leakage of cell enzymes and thus prevent the growth and spread of *E. coli* (Aluko et al., 2017; Li et al., 2018).

Salmonella is a food-borne pathogen that can cause serious illness in monogastric animals. Antimicrobial growth promoters have also been used extensively to minimize infection in swine and poultry. Several studies have shown that increasing *Lactobacillus* population and SCFA production are associated with the reduction in *Salmonella* (Adhikari et al., 2018; Bouwhuis et al., 2017). However, in addition to promoting mucosal barrier functions, the gut microbiota can also enhance the abovementioned pro- and anti-inflammatory cytokines. Therefore, the identification and characterization of more potential prebiotics in the gut microbiota alteration is necessary for future prebiotic studies.

6. Conclusions

A healthy GIT ecosystem is in a state of equilibrium, with its gut permeability, intestinal barrier function, and gut microbiota populations. Gastrointestinal health is influenced by a balanced gut ecosystem through the homeostasis of nutrient digestibility and absorption, immunomodulation, and gut microbiota alteration. Dietary supplementation with prebiotics in different stages has confirmed beneficial effects of prebiotics on host health, particularly in terms of protection against pathogenic bacteria (such as *Salmonella, E. coli,* and Clostridia) and increased levels of beneficial bacteria (such as bifidobacteria and *Lactobacillus*), thus inhibiting pathogen colonization and improving epithelial cell barrier functions. However, the observation of gut ecosystem variation throughout life can be a key strategy for host health. Recent studies revealed that prebiotic supplementation enhanced the probiotics in the gut ecosystem by creating favorable living conditions through colonic fermentation. In addition, cross-feeding approaches are gaining interest because a number of studies have found that some single probiotic strain does not grow as expected as in co-culture and fecal inoculum with prebiotics (Rawi et al., 2020; Sanders et al., 2019). With this knowledge, researchers will be able to further understand how gut microbes respond by different prebiotic substances to maintain the intestinal health of monogastric animals. In addition, it is also crucial to elucidate the effects of prebiotic on gut metabolite alterations during fermentation, bacterial gene expression, and their underlying mechanism. Furthermore, the identification and characterization of novel potential prebiotics would be a key pathway for future studies to promote host health. And, improving the precision and repeatability of the measures of microbial composition such as high-throughput techniques, which lead to actual, not misleading interpretations, are necessary in this field.

Author contributions

Jie Yin and Md A.K. Azad initiated the idea and outlined this paper. Md A.K. Azad and Jing Gao wrote the manuscript. Jie Yin, Jie Ma, Tiejun Li, Bie Tan, and Xingguo Huang provided intellectual oversight, suggestions and revised the paper. All authors read and approved the final manuscript.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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