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Review Article

Ferulic acid mediates prebiotic responses of cereal-derived arabinoxylans on host health

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A B S T R A C T

Dietary fiber is named as “the 7th nutrient” for humans, which is beneficial to improve intestinal health and prevent metabolic disease of the host. Mechanisms of dietary fiber administration on improved host health are mediated by short chain fatty acids (SCFA), which are reported to activate G protein-coupled receptors (GPR) and suppress activity of histone deacetylase (HDAC) to down-regulate expression of nuclear factor-κ-gene binding (NF-κB) signaling. Arabinoxylan is fermented by gut microbiota to produce SCFA and improved microbial community composition, intestinal barrier functions and host health. Interestingly, the latest publications have observed that ferulic acid combined with the arabinose in arabinoxylans from various cereal grains can be released through gut microbial fermentation. Ferulic acid can improve antioxidase activity and decrease reactive oxygen species (ROS) concentration by activating the signaling pathway of Kelch-like ECH-associated protein-1 and nuclear factor E2-related factor-2 (Keap1-Nrf2). However, the role of ferulic acid in cooperation with SCFA produced from microbial fermentation of cereal-derived arabinoxylan to regulate the intestinal health and host metabolisms, has been widely unclear. This review summarizes the potential mechanisms of ferulic acid from microbial fermentation of cereal-derived arabinoxylans on immunological functions and physiological metabolisms of the host. The evidence presented in the review indicates that dietary supplementation with cereal-derived arabinoxylans improves antioxidant capacity of intestinal epithelial cells due to the production of ferulic acid and SCFA from microbial fermentation. Ferulic acid can cooperate with SCFA to regulate intestinal integrity and immunological functions of the host. Peroxisome proliferator activated-receptor γ (PPARγ) may play an important role in integrating ferulic acid and SCFA to regulate host health and metabolism.

1. Introduction

Antibiotics have been widely used to prevent and cure enteric and infectious diseases caused by the pathogens in human nutrition and animal production. However, abuse of antibiotics can lead to many social and natural problems, such as occurrence of drug-resistant bacteria, food safety concerns and environmental pollution (Chewapreecha, 2013; Lin et al., 2020). To avoid a series of problems caused by abuse of antibiotics, prebiotics such as dietary fiber, organic acids, and plant essential oil, as antibiotic alternatives, have been gradually applied due to their positive responses on intestinal health, immunological functions, and energy metabolism of the host (Kasahara et al., 2018; Wang et al., 2019). Cereal-derived arabinoxylans have been universally accepted as the common prebiotic in the fields of human and animal nutrition (Nie et al., 2018; Suriano et al., 2017). Arabinoxylans as one of the primary fiber components contain a chain of linear β-D-xylopyranoside units, which can be substituted with α-L-arabinofuranosyl units through glycosidic linkages. Therefore, forms of feruloylated arabinoxylans are common in cereals and cereal by-products, and are partially or completely fermented by gut microbiota to produce

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short chain fatty acids (SCFA) with the release of free ferulic acid from arabinose residues (Pereira et al., 2021).

Short chain fatty acids produced by microbial fermentation of cereal-derived arabinoxylans mainly include lactic acid, acetic acid, propionic acid and butyric acid, which play an important role in regulating energy metabolism, immunological function and gut cell proliferation of the host (Koh et al., 2016). Many researchers have demonstrated that SCFA mediate inflammatory responses, glucose, and lipid homeostasis by activating G protein-coupled receptors (GPR), suppressing histone deacetylase (HDAC) and directly stimulating enteroendocrine L-cells to regulate integrity of the epithelial cells and production of pro- and anti-inflammatory cytokines, host defense peptides and hormones, resulting in improved intestinal barrier function and insulin sensitivity (Tolhurst et al., 2012; Smith et al., 2013). Overall, SCFA play a crucial role in regulating positive responses of cereal-derived arabinoxylans on host metabolisms and health.

Ferulic acid is combined with arabinose residues in cereal-derived arabinoxylans, but arabinoxylan is fermented by intestinal microbiota to release free ferulic acid, as well as production of SCFA (van Hung, 2016). Ferulic acid as one of the phenolic acids has a strong antioxidant capacity through activating the Kelch-like ECH-associated protein-1 and nuclear factor E2-related factor-2 (Keap1-Nrf2) signaling pathway to eliminate reactive oxygen species (ROS) and improve antioxidase activity (Mahmoud et al., 2020). A recent publication reported that cereal-derived arabinoxylans showed stronger antioxidant capacity compared with free ferulic acid, which indicated that there are some cooperative functions between ferulic acid and SCFA produced by microbial fermentation (Lin et al., 2014). However, the evidence is lacking to demonstrate the integrated molecular mechanisms of ferulic acid and SCFA on regulation of host health and metabolism. Therefore, our review summarized the potential mechanisms of cereal-derived arabinoxylans on regulating gut microbial composition, intestinal barriers, immunological function and energy metabolisms of the host. As reported, SCFA produced from microbial fermentation of arabinoxylan can activate GPR 43 and GPR 109A to suppress signaling pathway of nuclear factor-κ-gene binding (NF-κB) (Singh et al., 2014; Cleophas et al., 2016). The Nrf2 are activated by ferulic acid to improve host antioxidant capacity, however, expression of peroxisome proliferator activated-receptors (PPARγ) are down-regulated when Nrf2 genes are suppressed, which indicates that Nrf2 is an important transcriptional regulator of PPARγ signaling (Pi et al., 2010). In addition, the upregulation of PPARγ would suppress the activation of NF-κB to downregulate the expression of pro-inflammatory cytokines (Yin et al., 2013; Mao et al., 2012). Therefore, the evidence presented in our review indicates the signaling pathways of PPARγ play an important role in regulating responses of arabinoxylan on redox status, inflammatory response and energy metabolism of the host. In this review, we hypothesized that PPARγ acts as the link between SCFA and ferulic acid to regulate prebiotic effects of cereal-derived arabinoxylans.

2. Structure of feruloylated arabinoxylans

Arabinoxylan is a major type of non-starch polysaccharides (NSP) in cereal grains, such as wheat, corn, rye, barley, rice, oat and sorghum, and is involved in the formation of these cereals' epidermal tissues (Comino et al., 2016; Tian et al., 2015). The general structure of arabinoxylans contains a chain of linear (1,4)-β-D-xylopyranoside (Xylp) units, which can be substituted with α-L-arabinofuranosyl units through α-(1,2) or α-(1,3) glycosidic linkages (Gille and Pauly, 2012), therefore, arabinoxylans are always feruloylated in cereals and cereal by-products. There are mono- or di-substituted Xylp residues at the O-2 and O-3 positions and non-substituted Xylp residues. The L-arabinofuranose substitutions are mainly monomeric, although a small proportion of substitutions can form short oligomers, which consist of two or more arabinosyl residues or an arabinosyl residue with a terminal Xylp residue (Broekaert et al., 2011; Saulnier et al., 2007). In contrast, other substitutions include the linkage of glucuronic acids, uronic acids, D-galactose, D-glucose and acetyl residues to the Xylp backbone at the O-2 and/or O-3 position (Pastell et al., 2009).

3. Feruloylated arabinoxylan in cereals and cereal by-products

There is a large variation in the structure of feruloylated arabinoxylans among various cereal grains. Previous studies have reported that corn-derived and sorghum-derived arabinoxylans are more branched and have a higher amount of arabinose–xylose (A:X = 1.0 to 1.2) compared with barley (0.5 to 0.6), rye (0.4 to 0.5) and wheat (0.5 to 0.7), resulting in a greater proportion of ferulic acid in the branches connecting with arabinose residues (Bach Knudsen, 2014). Ferulic acid is one of the most abundant phenolic acids in cereals and cereal by-products (Wang et al., 2020). Ferulic acid derived from cereal and cereal by-products is present as 3 different forms, which are water-soluble (free status), fat-soluble and insoluble ferulic acids respectively (Shao et al., 2014). Water-soluble ferulic acid primarily exists in the pericarp of cereals and combines with small molecules, such as monosaccharides and disaccharides. Fat-soluble ferulic acid is present in the waxy layer on the surface of cereals, which connects with sterols and glutamine. Insoluble ferulic acid binds to fiber components and protein in the cereal cell wall with linkages of esters and ethers. In cereals, insoluble ferulic acid content is much higher than water-soluble and fat-soluble ferulic acids: the typical proportion of insoluble, water-soluble and fat-soluble forms of ferulic acid is 100:0.1:1 (Adom and Liu, 2002). Concentrations of ferulic acid in various cereals and cereal by-products are shown in Table 1.

4. Microbial metabolites of feruloylated arabinoxylans

Humans and animals do not secret endogenous digestive enzymes to degrade feruloylated arabinoxylan, but it can be fermented by intestinal microbiota in the caecum and colon to produce SCFA (Hald et al., 2016). Therefore, insoluble ferulic acid is primarily separated from cereal arabinoxylans through microbial fermentation in the intestine to release free ferulic acid which is then absorbed by the host. *Bacteroides* are the dominant bacteria in the proximal colon that degrade low branched arabinoxylans into feruloylated xylo-oligosaccharide with fewer degrees of polymerization (Pereira et al., 2021). Furthermore, *Bifidobacterium* and *Lactobacillus* are more inclined to degrade highly branched arabinoxylans or xylo-oligosaccharides (Long et al., 2019). The targeted metabolic activity of those dominant microfloras is supported by their preference to different chain lengths and substitution of arabinose on the main chain of xylan in arabinoxylans, resulting in a balance of the gut microecosystem in the host.

The intestinal epithelial cells can directly absorb water-soluble and fat-soluble ferulic acids in cereals into the blood circulation. However, the host cannot efficiently utilize insoluble ferulic acid, because it is combined with arabinoxylan in cereals. However, insoluble ferulic acid cannot be efficiently utilized by the host, since it is combined with arabinoxylan in cereals (Buranov and Mazza, 2009). Water-soluble and fat-soluble ferulic acids are dissolved in water or fat and are absorbed in the upper intestine, and insoluble ferulic acid is primarily fermented by gut microbiota in the hindgut, because the activity of fiber-degrading enzymes and feruloyl esterase secreted by gut microbiota are much higher

Table 1
Concentrations of arabinoxylans (AX) and ferulic acid in cereals and cereal by-products.[1]

Cereals	Tissue types	AX, %	Byproducts	Ferulic acid, mg/100 g
Corn	Bran	15 to 22	Corn bran	197 to 2,510
	Cob	24.6	Corn flour	232
Wheat	Endosperm	1.5 to 2	Wheat bran	63 to 445
	Bran	10 to 20	Wheat flour	45 to 125
Barley	Endosperm	1.8	Dehulled barley flour	30 to 40
	Bran	10.3	Hulled barley flour	60 to 100
Rye	Flour	4.4	Rye flour	15 to 25
Oat	Endosperm	1.2	Oat bran	16 to 45
	Bran	5.2	Oat flour	10 to 15
Rice	Endosperm	1.8	Unpolished rice	25 to 36
	Bran	6.8	Red unpolished rice	7.7
			Black unpolished rice	18 to 26
			White rice bran	130 to 180
			Red rice bran	68 to 112
			Black rice bran	106 to 116

[1] Data are adapted from Wang et al. (2020).

in the hindgut than these microflora in the foregut (Rose and Inglett, 2010). Rondini et al. (2004) compared the metabolism and absorption of pure ferulic acid and insoluble ferulic acid derived from wheat bran in a mouse model. The authors reported ferulic acid concentration in mouse's serum reached a peak sharply within 1 h and decreased to 0 at 4 h, however, when the mice were treated by insoluble ferulic acid the serum ferulic acid concentration remained at a low level for 24 h. This indicated that insoluble ferulic acids in cereals and cereal by-products are hydrolyzed by intestinal microbiota and released into the blood at a relatively slow speed, which has a more stable and efficient bioavailability than the intake of pure ferulic acid.

5. Responses of cereal arabinoxylans on host health mediated by SCFA

Microbial fermentation of cereal-derived arabinoxylans leads to the production of SCFA, primarily lactic acid, acetic acid, propionic acid and butyric acid. The activity of microbial fermentation to produce SCFA involves a series of principle reactions mediated by the composition and abundance of gut microbiota (Koh et al., 2016; Louis et al., 2014). Lactic acid is primarily produced in the upper gut from microbial fermentation of soluble polysaccharides and indigested oligosaccharides, but acetic acid, propionic acid and butyric acid are synthesized in the colon and cecum of the host. The localized production of SCFA is associated with a specific microbial community within the foregut and hindgut of the host (Zhao et al., 2019). In the foregut, *Lactobacillus* is the primary lactic acid-producing bacteria, however the abundance of *Lactobacillus* is reduced in the hindgut due to changes in the gut environment, such as pH and oxygen concentration. In addition, Prevotellaceae, Ruminococcaceae and Lachnospiraceae are rich in the hindgut and are dominant bacterial families that produce SCFA by microbial fermentation of cereal fibers (Liu et al., 2017). The intestinal epithelial cells can rapidly absorb the produced SCFA to influence gene expression, as well as cell differentiation and proliferation (Morrison and Preston 2016). Acetic acid is absorbed by the portal vein and acts as an energy source for muscle tissues while propionic acid is converted to glucose in the liver (Makki et al., 2018). Butyric acid is easily metabolized by β-oxidation in the mitochondria and provides from 60% to 70% of the total energy demand of colonic epithelial cells (Mentschel and Claus, 2003; Corrêa-Oliveira et al., 2016). In addition to being an important respiratory fuel, butyrate is considered beneficial for gut health of the host because it promotes proliferation of mucosa, differentiation of epithelial cells and colonic barrier functions in the host (Morrison and Preston, 2016). Potential molecular mechanisms of SCFA produced from microbial fermentation of arabinoxylans on host health and energy metabolism are shown in Fig. 1.

5.1. SCFA regulate intestinal microbiota community of the host

The SCFA facilitate microbial growth and bacteriocin secretion in the intestine, and enhance immune barrier and microbial barrier functions of the intestine, resulting in improved gut health of the host (Liu et al., 2018a,b). During microbial fermentation of cereal-derived arabinoxylans, the produced SCFA decrease pH of the intestinal environment and promote proliferation of intestinal epithelial cells (Morrison and Preston, 2016). The decreased pH provides a suitable growth environment for beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, and inhibits growth of harmful bacteria and invasion of pathogens. In addition, some differential bacteria shaped by microbial fermentation of cereal-derived arabinoxylans may secret bacteriocin to suppress growth of harmful bacteria and regulate the balance of gut microbial composition of the host. Bacteriocins lacticin and nisin, which are bacteriocins produced by strains of *Lactococcus lactis*, have been shown to be effective in vitro against clinically relevant diseases and disorders (Rea et al., 2013). Furthermore, treatment of cereal by-products, wheat bran and corn bran, increased the abundance of *Bacillus* in the hindgut of weanling pigs (Zhao et al., 2018a,b; Liu et al., 2018a,b). Most *Bacillus*, such as *Bacillus subtilis*, *Bacillus licheniformis* and *Bacillus amyloliquefaciens*, secret secondary metabolites of lipopeptides to inhibit growth and invasion of pathogens in the intestine, including surfactins, fengycins and iturins (Piewngam et al., 2018).

5.2. SCFA regulate immune functions and gut barrier of the host

The structural basis for intestinal digestion and nutrient absorption is the morphology of the intestinal mucosa, including the villus height and the crypt depth. Mucosa morphology reflects potential intestinal capacity for absorbing dietary nutrients. A decreased ratio of villus height to crypt depth usually means impaired digestion and absorption of nutrients by intestinal mucosa. Contrastingly, an increased ratio of villus height to crypt depth usually indicates improved intestinal mucosal function, and enhanced digestion and absorption of nutrients (Furuse, 2010). Many previous reports have shown that feruloylated arabinoxylans in cereal by-products stimulated the development of a host's intestine and resulted in an increased ratio of villus height to crypt depth in the intestine (Chen et al., 2014). One important reason for

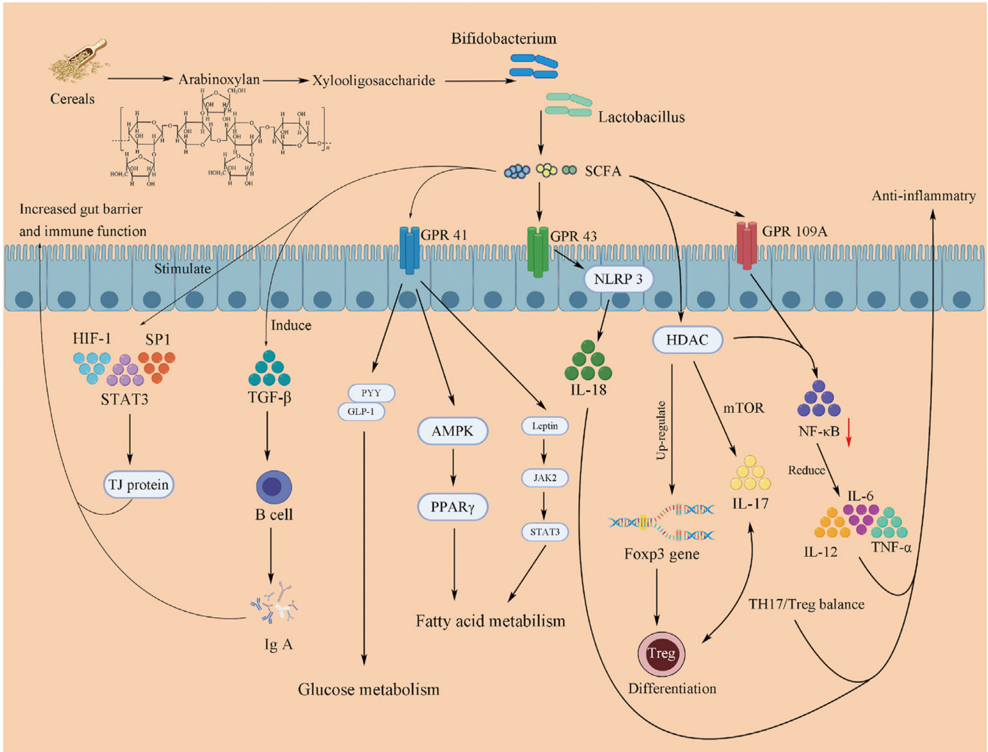

Fig. 1. Potential mechanisms of short-chain fatty acids (SCFA) produced from microbial fermentation of cereal arabinoxylans on host health and energy metabolism. SCFA directly induce expression of TGF-β to improve activity of intestinal lymphocyte cells and concentration of secretory immunoglobulin A (sIgA). In addition, SCFA directly enhance expression of tight junction proteins, proliferation and differentiation of intestinal epithelial cells by activating JAK/STAT3. SCFA inhibit activity of HDAC and stimulate expression of G protein-coupled receptors (GPRs) to regulate immune function. Butyric acid activates GPR 109A on the antigen-presenting cells in the colonic macrophages to promote secretion of pro-inflammatory cytokines, resulting in the differentiation of T regulatory cells and the improved secretion of interleukin-10. SCFA activate NLRP-3 by identifying GPR 43 to suppress expression of IFN-γ and IL-18, leading to an improvement of intestinal immune. AMPK = AMP-activated protein kinase; AP-1 = activator protein-1; GLP-1 = glucagon-like peptide-1; HDAC = histone deacetylase; IFN-γ = interferon-γ; JAK = Janus kinase; IL = interleukin; NF-κB = nuclear factor-κ-gene binding; NLRP-3 = pyrin domain containing protein-3; PPARγ = peroxisome proliferator activated-receptor γ; PYY = peptide YY; STAT-3 = signal transducer and activator of transcription-3; TGF-β = transforming growth factor-β; TJ protein = tight junction protein; TNF-α = tumor necrosis factor-α.

improved intestinal morphology induced by cereal-derived arabinoxylans is that microbial fermentation of arabinoxylan directly disrupts the surface structure of the mucosal layer and increases the speed of cell shedding, which causes compensatory growth of mucosal cells. In addition, the produced SCFA in the host's intestine reduce the pH of the gut and stimulates cell division and cell proliferation (Tan et al., 2014). Meanwhile, SCFA simulate the secretion of gastrin and glucagon-like peptides, which boost the proliferation of epithelial cells in the host intestine (Tolhurst et al., 2012). Specifically, butyric acid provides energy for proliferation of epithelial cells in the host intestine and modifies gene expression for epidermal growth factors and repairs damaged epithelial cells, which would promote intestinal morphology and development (Koh et al., 2016; Liu et al., 2018a,b).

The intestinal mucosal barrier is composed of physical, chemical, immunological and microbial barriers. The mucosal barrier mainly consists of tight junction proteins, mucins, intestinal trefoil peptides, antimicrobial peptides, inflammatory cytokines and secretory immunoglobulin A (sIgA). There is much evidence that the intake of feruloylated arabinoxylans increases the expression of tight junction proteins, secretion of mucins and activation of intestinal immune cells mediated by the SCFA produced as a result of arabinoxylan (Tong et al., 2016; Peng et al., 2009). Vila (2017) observed that the intake of cereal by-products, corn bran and wheat bran, significantly improved mucin-2 level in the ileal and colonic mucosa of pigs. Weanling piglets provided a diet supplemented with feruloylated arabinoxylan had significantly increased sIgA secretion in the intestine and a greater number of goblet cells, in combination with reduced intestinal permeability (Chen et al., 2013). Furthermore, many researchers have reported that the produced SCFA are beneficial to secretion of mucosal proteins in pig intestine, but the concentrations and types of SCFA can also influence the expression of mucosal proteins (Barcelo et al., 2000). Hatayama et al. (2007) reported that butyric acid, rather than acetic acid and propionic acid, stimulates mucins production in human colon cancer cell lines. Fundamentally, the intake of feruloylated arabinoxylan could increase food intake and flow of the digesta in the intestine, which promotes renewal of mucosal protein, thus affecting the intestinal mucosal layer. Moreover, fermentation of feruloylated arabinoxylan stimulates intestinal epithelial cells to secret mucosal protein, and produce growth factors and metabolites such as arachidonic acid, all of which are beneficial to goblet cell proliferation and mucosal protein secretion (Mcrorie and Mckeown, 2017).

The produced SCFA play an important role in improving intestinal immune barriers and intestinal permeability by regulating the secretion of inflammatory cytokines, expression of tight junction proteins and activation of immune cells of the host. Firstly, SCFA direct induce the expression of transforming growth factor-β (TGF-β) to improve the activity of intestinal lymphocyte cells and concentration of sIgA (Furusawa et al., 2013). In addition, SCFA directly improve the expression of tight junction proteins, and proliferation and differentiation of intestinal epithelial cells by activating Janus kinase/signal transducer and activator of transcription-3 (JAK/

STAT3) (Zhao et al., 2018a,b). The produced SCFA have been reported to modulate the immune function of the host by inhibiting the activity of HDAC and stimulating the expression of GPRs (Smith et al., 2013). Sodium butyrate regulates the release of interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) by inhibiting HDAC activity and activating the activator protein 1 (AP-1) signaling pathway to enhance the intestinal immune function of the host (Cox et al., 2009; Tan et al., 2014). At the same time, sodium butyrate effectively regulates the function of T lymphocytes through activating GPR 43 to reduce the level of inflammatory factor IL-2 and to increase the secretion of anti-inflammatory factor interleukin-4 (IL-4) and antimicrobial peptide LL-37, which ultimately inhibits the inflammation response of the host (Macpherson et al., 2008; Cleophas et al., 2016). In addition, butyric acid activates GPR 109A on the antigen-presenting cells in the colonic macrophages to promote the secretion of pro-inflammatory cytokines, resulting in the differentiation of T regulatory cells and the improved secretion of interleukin-10 (IL-10) (Singh et al., 2014). Further, SCFA can activate pyrin domain containing protein-3 (NLRP3) inflammasome by identifying GPR 43 to suppress expression of interferon-γ (IFN-γ) and IL-18, leading to an improvement of intestinal immunity (Macia et al., 2015). Overall, SCFA produced from fermentation of feruloylated arabinoxylan play a crucial part in improving intestinal barrier and immune functions of the host by inhibiting the activity of HDAC and stimulating the expression of GPR to down-regulate activation of NF-κB.

5.3. SCFA regulate glucose and fatty acid metabolisms of the host

Studies have reported that fat tissue of the body and visceral fat weights were reduced in hosts treated by a diet supplemented with arabinoxylan or xylo-oligosaccharide (Chunchai et al., 2018; Long et al., 2019). Dietary supplementation with xylo-oligosaccharide to a high-fat diet significantly decreased fasting blood glucose level and alleviated obesity associated glucose intolerance, suggesting an important role of xylo-oligosaccharide in improving insulin sensitivity (Gobinath et al., 2010). Many studies have reported that SCFA, the primary microbial metabolites, mediate glucose homeostasis and fat acid metabolism in the host by activating GPR 41 and 43 and stimulating enteroendocrine L-cells to produce glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), both increasing the insulin sensitivity (Gao et al., 2009; Tolhurst et al., 2012). Activation of GPR by SCFA increases activity of AMP-activated protein kinase in the liver and muscle, which in turn activates PPARγ and coactivator-1α (PGC-1α), resulting in improved oxidation of fatty acid and reduced fat accumulation (Besten et al., 2015). SCFA can also promote expression of leptin receptor, Janus kinase-2, signal transducers and activation of transcription-3 (STAT-3) in adipose tissue, resulting in an increase in fatty acid hydrolysis (Kebede et al., 2009).

Microbial fermentation of dietary NSP, like cereal-derived arabinoxylan, leads to large amounts of SCFA being released in the colon, which could protect non-obese diabetic mice from the onset of diabetes (Marino et al., 2017). This suggests that the SCFA produced play an important role in preventing the risk of type I diabetes mellitus. As reported by many previous studies, the protection from diabetes provided by SCFA is probably associated with the activation of the GPR on the intestinal and hepatic cells of the host to regulate tolerance of glucose and insulin sensitivity (Tang et al., 2015). In summary, consumption of feruloylated arabinoxylan is a promising strategy to regulate glucose and fatty acids metabolism, and prevent human obesity and diabetes, through the activation of cellular receptors of GPR *via* produced SCFA (Zhao et al., 2018a,b). More interestingly, a combination of acetic acid and butyric acid provided a more effective protection for susceptible patients from type I diabetes mellitus, which suggested that the different types of SCFA contribute to protection *via* a distinct mechanism (Marino et al., 2017). However, the variable molecular mechanisms of different types of SCFA on regulating glucose metabolism and preventing metabolic diseases have not been extensively studied. Furthermore, there are conflicting findings on the beneficial responses of SCFA on glucose and fat metabolism in humans, and further well-controlled long-term intervention studies should be conducted to verify how SCFA regulate metabolic diseases of the host (Canfora et al., 2015).

In addition, much evidence has demonstrated that glucose metabolism and homeostasis of the host are directly associated with intestinal microbial composition shaped by feruloylated arabinoxylan supplementation (Delgado and Tamashiro, 2018). An intolerance of glucose can be improved after xylo-oligosaccharide administration in a diabetic rat model, which was related to increased abundance of *Bifidobacterium* and *Lactobacillus* (Gobinath et al., 2010). However, the molecular mechanisms of the differential intestinal microbiota, and how they regulate glucose metabolism of the host have been unclear. To clarify whether gut microbial metabolites play an important role in host metabolism mentioned above, metabonomics technologies have been gradually developed and implemented in the field (Zhang et al., 2014; Wen et al., 2019). A previous study reported that production and accumulation of sphingolipids in obese patients would impair insulin signaling, leading to insulin resistance and promotion of other metabolic diseases (Staneva et al., 2014). Furthermore, dietary xylo-oligosaccharide supplementation could affect lipid compositions of hepatic membranes by altering concentration of sphingolipids. The evidence above indicates that feruloylated arabinoxylan and xylo-oligosaccharide would be able to mediate production of sphingolipids, however, the potential molecular mechanisms are unknown.

6. Responses of cereal arabinoxylans on host health mediated by ferulic acid

Ferulic acid is a major phenolic acid in cereals and cereal by-products and can act as a natural antioxidant to eliminate free radicals (Levigne et al., 2004). In a structure of feruloylated arabinoxylans, ferulic acid is usually connected with C-2 and C-5 positions of L-arabinofuranosyl residues or C-4 of D-xylopyranosyl residues. Cereal-derived arabinoxylans are commonly degraded by *Bacteroidetes* to feruloylated oligosaccharides, which are further fermented by *Bifidobacterium* and *Lactobacillus* to produce SCFA and free ferulic acid (Tremaroli and Bäckhed, 2012). Ferulic acid has a broad anti-bacterial spectrum, in which its mechanism is a reduction of intracellular pH and imbalance of the polarity on the cell membrane surface, leading to the destruction of cell membrane functions in pathogens (Shi et al., 2016). Potential molecular mechanisms of ferulic acid on antioxidant capacity and immune function of the host are shown in Fig. 2. Some previous studies have reported that ferulic acid inhibits activity of human immunodeficiency virus type-1 (HIV-1) integrase, genetic replication and reverse transcription of HIV-1, which indicated that ferulic acid has an anti-viral property, in addition to an anti-bacterial function (Sanna et al., 2018; Sonar et al., 2017). Furthermore, ferulic acid improves antioxidase activity to eliminate ROS and release damage of oxidant Nrf2 signaling to match the antioxidant response element (ARE) (Zhang et al., 2015). Mahmoud et al. (2020) reported ferulic acid decreased concentrations of ROS, malonyldialdehyde (MDA) and nitric oxide (NO) in the liver tissue of mice treated with methotrexate, resulting in a reduction of liver damage. Meanwhile, ferulic acid could improve the activity of superoxide (SOD), catalase (CAT) and glutathione peroxidase (GPX) in the intestine of mice, and is beneficial to mitochondrial functions and in reducing

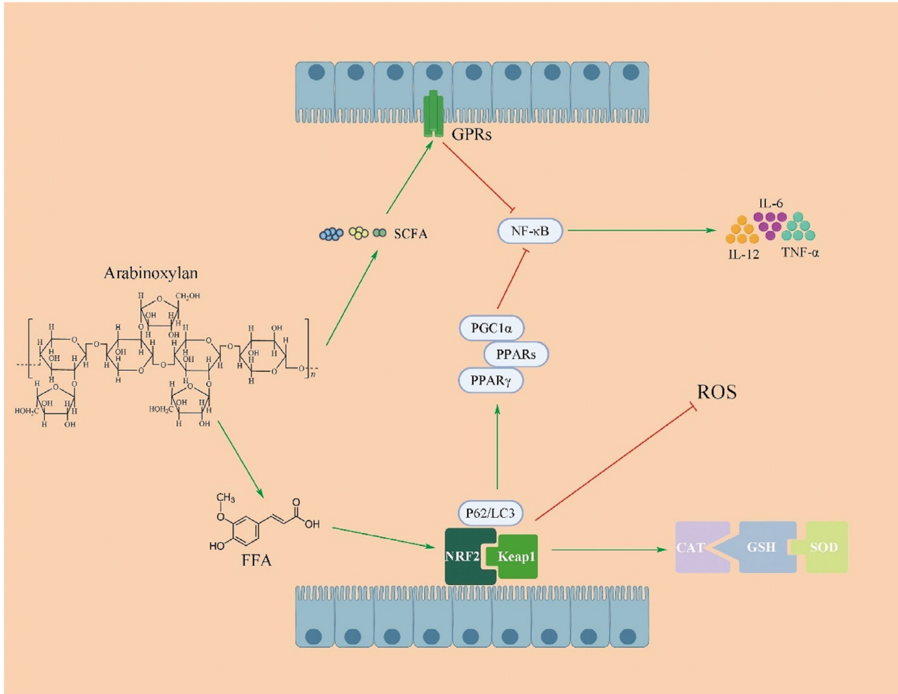

Fig. 2. Potential mechanisms of ferulic acid on antioxidant capacity and immune function of the host. Ferulic acid improves antioxidase activity to eliminate reactive oxygen species (ROS) and release damage of oxidant stress by activating nuclear factor E2-related factor-2 (Nrf2) signaling to match antioxidant response element (ARE). Ferulic acid down-regulated expression of NF-κB in vascular smoothing muscle cells, resulting in a decrease TNF-α, IL-1β and IL-6 concentrations. The potential mechanism of ferulic acid to suppress activation of NF-κB is to hinder phosphorylation of NF-κB-inhibitor kinase. CAT = catalase; FFA = free ferulic acid; GSH = glutathione peroxidase; GPR = G protein-coupled receptors; Keap-1 = Kelch-like ECH-associated protein-1; IL-2 = interleukin-2, IL-6 = interleukin-6, MDA = malonyldialdehyde; PGC-1α = coactivator-1α; PPARγ = peroxisome proliferator activated-receptor γ; SCFA = short-chain fatty acids; SOD = superoxide; TNF-α = tumor necrosis factor-α.

oxidative stress of arterial and epithelial cells. In addition, ferulic acid is involved in the regulation of inflammatory responses in the host by acting on NF-κB signaling. Chowdhury et al. (2019) found 50 mg/kg body weight of ferulic acid decreased expression of proinflammatory cytokines in the kidney of mice, and is beneficial to immunological regulation and protective autophagy responses of the kidney. Ferulic acid down-regulated expression of NF-κB in vascular smoothing muscle cells, resulting in a decrease TNF-α, IL-1β and IL-6 concentrations (Cao et al., 2015). The potential mechanism of ferulic acid to suppress activation of NF-κB is to hinder phosphorylation of NF-κB-inhibitor kinase (Shin et al., 2011). In addition, ferulic acid as one of the natural phenolic acids, acts to regulate glucose and fat metabolisms, affecting metabolic diseases of the host. Ferulic acid decreased concentrations of total triglyceride, total cholesterol, low density lipoprotein cholesterol, free fatty acids, glucose and insulin in serum when mice were provided a diet with high fat and high glucose, resulting in improved glucose tolerance and insulin resistance (Wang et al., 2015). The actions of ferulic acid in regulating host energy metabolisms are primarily to reduce the concentration of leptin and lipase activity, resulting in lower food intake. The molecular mechanisms of ferulic acid to the metabolic disorders of the host are the activation of AMP-activated protein kinase (AMPK) and the improved phosphorylation of protein kinase B, leading to an improved insulin activity and decomposition of carbohydrates and fatty acids. In addition, ferulic acid down-regulated the expression of diacylglycerol acyltransferase gene (DGAT-1) to suppress synthesis of fatty acids (Guo et al., 2015). A recent study has shown that ferulic acid can regulate the balance of glucose and fatty acid metabolisms by maintaining the self-renewal of embryonic stem cells and adipose tissue-derived mesenchymal stem cells in mice (Cho et al., 2019). Finally, ferulic acid alleviated symptoms of cardiac hypertrophy following clinical surgery, which may be regulated by inhibiting protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) signaling pathway (Zheng et al., 2012).

7. Synergetic interactions between SCFA and ferulic acid on host health

Cereal-derived arabinoxylans are fermented by intestinal microbiota to feruloylated xylo-oligosaccharide, and then further degraded to produce SCFA and free ferulic acid. Much evidence has shown feruloylated xylo-oligosaccharide can eliminate free oxygenic radicals, prevent lipid oxidation of microsome and inhibit hemolysis of red blood cell induced by free radicals, and that has stronger antioxidant capacity compared with vitamin C or free ferulic acid (Lin et al., 2014). Those findings indicate that there may be some potential interactions on antioxidant capacity of the host between free ferulic acid and SCFA, both of which are produced by microbial fermentation of cereal-derived arabinoxylans. As mentioned above, SCFA, especially butyric acid can activate GPR 43 and GPR 109A to regulate inflammatory responses of the host by suppressing NF-κB signaling. Furthermore, free ferulic acid improves antioxidant capacity of the host *via* activating signaling pathway of kelch-like ECH-associated protein-1 and Keap1-Nrf2. The PPARγ is a class of ligand, which is activated by nuclear transcription factors. Previous studies have shown that the expression of PPAR γ gene is also down-regulated when Nrf2 is knocked out or its activity is inhibited, suggesting that Nrf2 is an important transcriptional regulator of the PPARγ signaling pathway (Pi et al., 2010). Some publications have reported that rosiglitazone, an agonist of PPARγ, enhanced PPARγ gene expression in a colitis mouse model and down-regulated NF-κB and TNF-α expressions, which indicated that PPARγ could competitively inhibit the activation of NF-κB (Mao et al., 2012). In addition, activation of GPR by SCFA increases the activity of AMP-activated protein kinase in the liver and muscle, which in turn activates PPARγ and PGC-1α, resulting in improved oxidation of fatty acid and reduced fat accumulation (Gabler et al., 2008). Therefore, signaling pathways of PPARγ, which can be mediated by both of SCFA and ferulic acid, play important roles in regulating antioxidant capacity, immunological function and fatty acid metabolism of the host (Fig. 2). Based on the evidence mentioned above, we hypothesize that arabinoxylans interact to influence host health and metabolism where ferulic acid, isolated from ferulated arabinoxylans, activates PPARγ through the regulation of Keap1 − Nrf2 signaling and suppresses phosphorylation of NF-κB signaling in cooperation with SCFA. However, our hypothesis that PPARγ acts as the link between SCFA and ferulic acid to regulate the prebiotic effects of cereal-derived arabinoxylans should be further verified.

8. Conclusion

In summary, cereal-derived arabinoxylans have been demonstrated to play a vital role in regulating gut microbial community, intestinal barrier, immunological functions, and glucose and fatty acid metabolisms in the host. At present, the mechanism of action of arabinoxylans on host health and metabolism are through the activation of GPRs or inhibition of HDAC activity to suppress NF-κB signaling as mediated by SCFA produced from microbial fermentation. Cereal-derived arabinoxylans are usually fermented by intestinal microbiota to produce free ferulic acid, as well as SCFA, and ferulic acid shows prebiotics effects on antioxidant capacity and inflammatory responses of the host through activation of the signaling pathway of Nrf2. Signaling pathways of PPARγ, which can be mediated by both SCFA and ferulic acid, play important roles in regulating antioxidant capacity, immunological functions and energy metabolism of the host. Based on the published evidence, we put forward that ferulic acid and SCFA, produced from microbial fermentation of cereal-derived arabinoxylans, interact to influence host health and metabolism. Further investigation into the role of PPARγ in connecting SCFA and ferulic acid would be beneficial to advance the current understanding of the molecular mechanisms of cereal-derived arabinoxylans in regulating host health.

Author contributions

Zeyu Zhang: Conceptualization, Software, Data Curation, Writhing-Original Draft Preparation, and Visualization; **Zeyu Zhang and Pan Yang**: Methodology; **Pan Yang**: Investigation; **Jinbiao Zhao**: Supervision, Validation, Writing- Reviewing and Editing.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and 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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