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Review Article

Research progress on anti-stress nutrition strategies in swine

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ABSTRACT

In swine production, stress is a common encounter that leads to serious bacterial infection and adverse effects on growth performance. Though antibiotics have been frequently used to control pathogen spread, sustained negative impacts from antibiotics have been found to affect intestinal integrity and the immune system. Multiple nutritional strategies have shown potential to counteract stress and replace antibiotics, including functional amino acids, low protein diet, plant extracts, organic acids, prebiotics, probiotics, minerals and vitamins. These additives relieve the stress response in swine via different mechanisms and signal transduction pathways. Based on the overview of signaling pathways and stress models, this review highlights the potential of nutritional strategies in swine for preventing or treating stress-related health problems. For wider application in the pig industry, the dose ranges measured require for further validation in different physiological contexts and formulations. In the future, microfluid devices and novel stress models are expected to enhance the efficiency of screening for new anti-stress candidates.

1. Introduction

In farms, pigs are subjected to a variety of stimuli, from diseases and vaccination (Martinez-Miro et al., 2016), weaning (Pluske et al., 1997), transportation (Tarrant. 1989; Peeters et al., 2004), pregnancy and parturition (Jain, 2016; Hao et al., 2021), that trigger a strong stress response and inflammatory reaction in the body (Hao et al., 2021). Poor welfare conditions also lead to psychological and physical distress in farms, where pigs experience sudden temperature changes (Gonzalez-Rivas et al., 2020; Yang et al., 2021c), uncomfortable housing management (Ramirez et al., 2022), aggressive manual handling (Health et al., 2022) and overcrowded systems (Wolter et al., 2003; Kemp et al., 2012). After stimulation, an organism produces a series of biomarkers, such as reactive oxygen species (ROS) (Wang et al., 2017), malondialdehyde (MDA) (Rio et al., 2005), cortisol, and immunoglobulins (Ig) (Martinez-Miro et al., 2016). Under these conditions, the immune function and intestinal permeability of piglets are likely to be disrupted (Modesto et al., 2009), causing diarrhea or growth retardation (Gaggia et al., 2010; Upadhaya et al., 2021). Transportation stress is an important factor for meat quality through accelerating muscle glycogenolysis and decreasing water holding capacity (Briskey. 1964; Peeters et al., 2006; Gonzalez-Rivas et al., 2020). Heat-stressed sows, particularly during gestation, present with hyperpnea, constipation, severe metabolic burden and depressed litter size (Lucy et al., 2017) (Fig. 1).

1.1. Stress induction models in pigs

In the past, a variety of models have already been established to study stress responses, including the lipopolysaccharide (LPS) model, hydrogen peroxide (H_2O_2) model, diquat model and mycotoxin model (Hao et al., 2021). LPS, a primary constituent of the outer surface membrane of Gram-negative bacteria (Meissner et al., 2013), can induce inflammatory responses, oxidative stress

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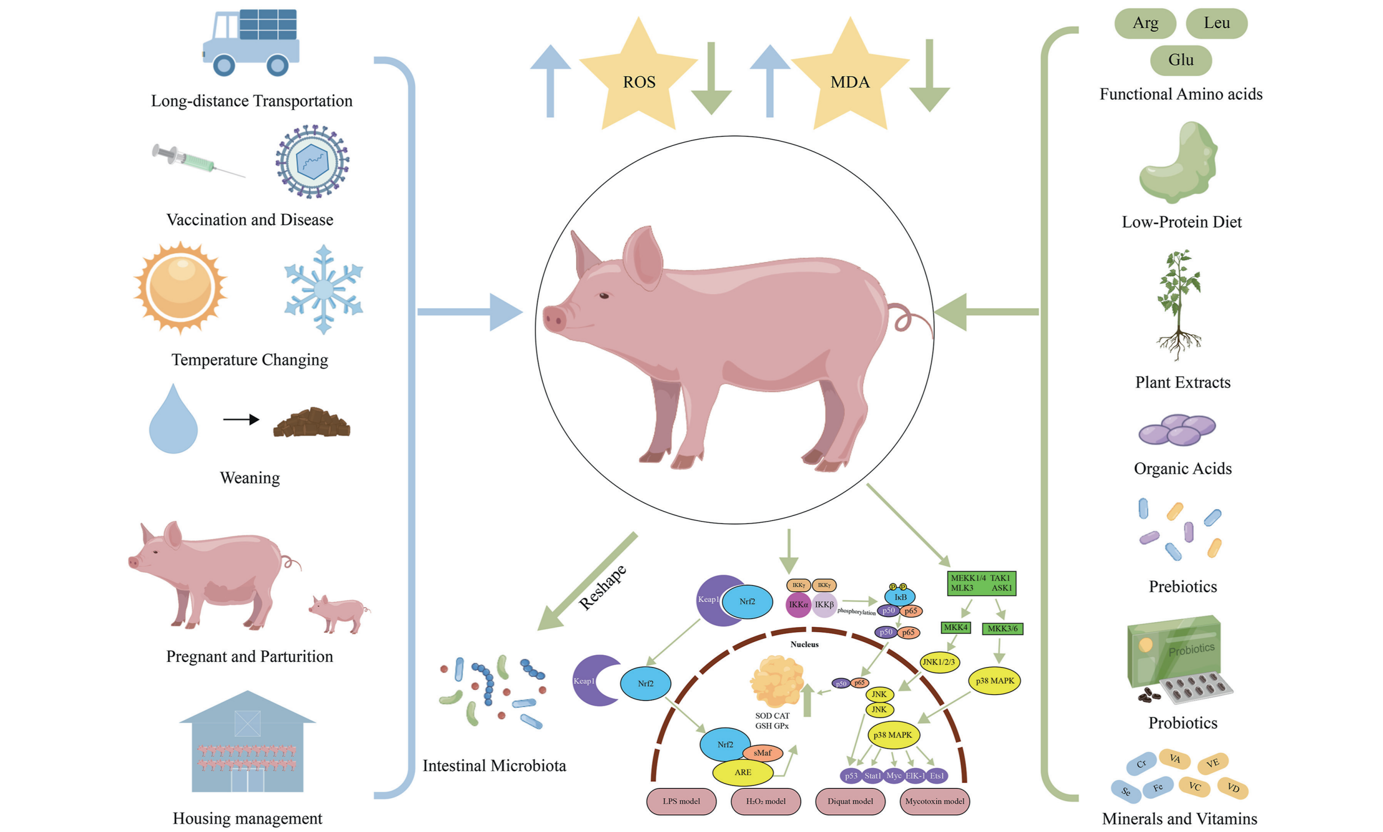

Fig. 1. Stress factors and nutritional strategies in pig production. Common stress factors, such as long-distance transportation, vaccination and disease, temperature changes, weaning, pregnancy, parturition and housing management could lead to increases in ROS and MDA in swine. A variety of models have already been established to study stress responses, including the LPS model, H_2O_2 model, diquat model and mycotoxins model. The nutritional strategies refer to functional amino acids, low protein diets, plant extracts, organic acids, prebiotics, probiotics, minerals and vitamins, which reshape the microbiome, activate the Keap1/Nrf2, NF-κB and MAPK pathways and enhance the activity of SOD, CAT, GSH and GPx. ARE = antioxidant response element; ASK1 = apoptosis signal-regulating kinase 1; CAT = catalase; ElK = ETS-like transcription factor; GPx = glutathione peroxidase; GSH = glutathione; IKK = IκB kinases; JNK = c-Jun N-terminal kinases; Keap1/Nrf2 = Kelch-like epichlorohydrin-associated protein 1/nuclear factor erythroid 2-related factor 2; MAPK = mitogen-activated protein kinase; MDA = malondialdehyde; MEKK = mitogen-activated protein kinase kinase kinase; MKK = mitogen-activated protein kinase kinase; MLK = mixed lineage kinase; LPS = lipopolysaccharide; ROS = reactive oxygen species; sMaf = small Maf proteins; Stat1 = signal transducer and activator of transcription 1; SOD = superoxide dismutase; TAK1 = transforming growth factor-β activated kinase 1; VA = vitamin A; VC = vitamin C; VD = vitamin D; VE = vitamin E.

and tissue damage in swine (Xia et al., 2018). In LPS-induced piglets, plasma pro-inflammatory cytokines, such as interleukin-6 and interleukin-1β, were increased (Jia et al., 2015). High STEAP4 expression in piglets was found to be involved in cellular regulation and immunological stress (Xia et al., 2018). In addition, H_2O_2 could activate nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) in swine (Yin et al., 2015a, 2017). In a porcine ex vivo retina culture model, Hurst et al. (2017) utilized H_2O_2 at 300 μM to induce oxidative stress. In vivo, Yin et al. (2017) found that the intragastric administration of 5% H_2O_2 modulated the intestinal toll-like receptor (TLR) system and apoptosis to induce oxidative stress. As a common commercial herbicide, diquat also induces oxidative stress at a certain concentration in vivo and in vitro (Wang et al., 2019a; Hao et al., 2021). Through an intraperitoneal injection of diquat at 10 mg/kg in piglets, mitochondrial disorders and destruction of the intestinal barrier were induced by excessive ROS (Cao et al., 2018). Moreover, diquat-induced oxidative stress also leads to the differential expression of long noncoding RNAs and mRNAs in livers of piglets (Wang et al., 2019a). In intestinal porcine epithelial cell lines J2 (IPEC-J2), diquat at 40 μg/mL was adopted to induce oxidative stress by activating the NF-κB signaling pathway (Bao et al., 2021; Cai et al., 2022). In naturally contaminated diets, each additional 1 mg/kg deoxynivalenol leads to growth depression of approximately 8% in pigs (Bell et al., 2002).

1.2. Signaling pathways and gene expression during stress

For signaling pathways, signaling molecules in the Kelch-like epichlorohydrin-associated protein 1 (Keap1)/Nrf2 signaling pathway (Costilla et al., 2019; Zhou et al., 2020b), NF-κB (Kianian et al., 2022), mitogen-activated protein kinase (MAPK) (Lee et al., 2020), AMP-activated protein kinase (AMPK) (Yang et al., 2018a, 2018b) and PTEN/phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) (Chen et al., 2022a; Sun et al., 2022) pathways have been verified to modulate the expression of relevant redox genes to alleviate or activate stress progression in swine (Hao et al., 2021). Nrf2 binds to the antioxidant response element to upregulate the expression of genes encoding phase II detoxification or antioxidant enzymes (Itoh et al., 1997; Motohashi et al., 2004; Cho et al., 2006; Hyeon et al., 2013). Meanwhile, Keap1 can prevent ubiquitination degradation of Nrf2 (Yu and Xiao, 2021). The activation of the p38 MAPK signaling pathway can inhibit apoptosis during stress (Diamond-Stanic et al., 2011; Shin et al., 2011; Liu et al., 2012; Supanji et al., 2013). NF-κB is a class of transcription factors (Hayden et al., 2008; Vallabhapurapu et al., 2009) which increase the expression of antioxidant proteins and regulate the ROS level (Morgan et al., 2011). In inflammatory reactions, the NF-κB and MAPK signaling pathways are both activated (Lugrin et al., 2014). As a master regulator of inflammation (Cai et al., 2022), NF-κB is regulated by IκB kinase via IκB phosphorylation (Lawrence. 2009;

Chen et al., 2018c). Stress further activates c-Jun N-terminal kinases (JNK), leading to phosphorylation of p38 transcription, and initiation of inflammatory cytokines in the nucleus (Raingeaud et al., 1996; Pearson et al., 2001; Sabio et al., 2014) (Fig. 1).

1.3. Stress and intestinal barrier function

The intestine is a main organ of nutrition digestion and absorption (Isaacson et al., 2012). Through a physical barrier, chemical barrier and immune barrier, the intestinal mucus layer serves as a defense line against the invasion of bacteria, endotoxins and antigens in response to stress (Tang et al., 2016; Li et al., 2018). Structurally, as weaning stress and oxidative stress weaken the multiple mucins and tight junction proteins, the morphology of the small intestine changes obviously, with decreased villus height and increased crypt depth (Cao et al., 2022). Functionally, bacterial endotoxins and antigen proteins tend to break through a compromised mucosal barrier by pattern recognition receptors, eliciting a release of pro-inflammatory cytokines including interleukin-1β, tumor necrosis factor-α (TNF-α), and IFN-γ (Lee et al., 2017; Tang et al., 2022). Enteric tract infections decrease the activity of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase, which are ion pumps that maintain ion balance, in pig small intestinal epithelial cells (Wang et al., 2019d).

The use of antibiotics is a common treatment for bacterial infection. However, studies have shown that antibiotics result in negative effects on the development of the immune system and a sustained state of increased gut permeability in newborn mammals (Fouhse et al., 2019; Wang et al., 2020b; Westrom et al., 2020). The long-term or improper use of antibiotics in swine permanently contributes to dysbiosis of the gut microbiome, which is reflected in the increase of antibiotic-resistant microbes and the loss of microbiome diversity (Ubeda et al., 2010; Looft et al., 2012; Perez-Cobas et al., 2013). As antibiotic regulations arise, environmentally friendly alternatives are urgently needed in the breeding industry (Landers et al., 2012).

Nutritional interventions are effective strategies to limit or alleviate the degree of health problems and unnecessary growth losses, especially for oxidative stress and pathogenic infection (Lauridsen. 2019). In recent decades, functional amino acids, low protein diet, plant extracts, organic acids, prebiotics, probiotics, minerals and vitamins have received increasing attention. These measures show potential to reshape the composition of the gut microbiota, improve intestinal barrier function and nutrient absorption as alternatives to antibiotics. In this review, classic stress models in pigs and the potential action mechanisms of aforementioned substances are clarified and discussed.

2. Nutritional strategies during stress

2.1. Functional amino acids

Traditionally, amino acids have been classified as essential amino acids and nonessential amino acids, according to the net synthesis of protein in the whole body (Baker, 2009; Wu, 2009). Besides the role as building blocks of proteins, some amino acids play functional roles in improving survival, growth, development, immunity, lactation and reproduction of organisms via key metabolic pathways (Wu, 2010, 2013). Common functional amino acids consist of arginine, glutamate, leucine, tryptophan, glutamine, proline, cysteine, methionine, threonine, aspartic acid, asparagine and glycine (Wu, 2009) (Table 1).

Dietary amino acid levels are important for the quality of embryos in sows in the first trimester (Bell et al., 2002; Duan et al., 2019b). Arginine was reported to induce the production of nitric oxide and blood perfusion. The process improves uterine capacity and foetal growth in late pregnancy (Novak et al., 2012; Langendijk, 2021). Arginine is required in all phases of pig development, from weaning, finishing, gestating, to lactation (Mateo et al., 2008; Tan et al., 2009; Wu et al., 2015, 2018). Lack of arginine could lead to hyperammonemia and even death in piglets (Brunton et al., 1999). Supplementation with 1.5% arginine in the sow diet in the late gestational period increased blood arginine and ornithine concentrations of sows, and the survival of newborn piglets (Hong et al., 2020). In weaning piglets exposed to heat stress, dietary supplementation with 0.4% arginine significantly alleviated the losses of average daily gain and feed efficiency (Yun et al., 2020). The arginine family amino acids are involved in antioxidant capacity, including arginine, glutamate, glutamine, and proline (Wu et al., 2007; Wu, 2014). Pro-oxidants such as diquat induced oxidative damage, which was attenuated through supplementation of 1.6% L-arginine in diets of weaned piglets by increased activity of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in plasma (Zheng et al., 2013). For boars under high ambient temperature, a basal diet supplemented with 0.8% or 1.0% L-arginine (wt:wt) improved the fertility and semen antioxidant capacity (Chen et al., 2018b). In growing pigs, dietary supplementation with arginine and lysine significantly inhibited the level of plasma cortisol during transportation stress (Srinongkote et al., 2003).

Glutamate is abundant in sow milk during lactation (Wu et al., 2011), but glutamate concentration is relatively lower in plasma in weaning piglets compared with other amino acids (Flynn et al., 2000). In post-weaning piglets, supplementation with 4% monosodium glutamate increased glutamate concentration in plasma, daily weight gain and feed efficiency (Rezaei et al., 2013). As a major fuel for intestinal mucosa (Burrin et al., 2009), glutamate improves intestinal barrier homeostasis (Rezaei et al., 2013), as well as growth performance and survival of weaning piglets (Hou et al., 2018). Glutamate is a precursor of glutathione (GSH), protecting organs from oxidative stress (Ren et al., 2014b; Duan et al., 2016). Lack of glutamate inhibits cell proliferation by the mechanistic target of rapamycin-ribosomal S6 kinase (mTOR/S6K1) pathway, which might lead to disturbance of intestinal epithelial renewal in neonatal pigs (Li et al., 2016a). For weaned pigs challenged with LPS, supplementation of 2% glutamate decreased mast cell number and increased intestinal intraepithelial lymphocyte number, attenuating intestinal histology (Guo et al., 2022). After challenge with H_2O_2, supplementation with 2% glutamate in the diet preserved the spermatogonium integrity and relieved testicular swelling for boars (Tang et al., 2020).

Among branched chain amino acids, leucine is regarded as the most important regulator of muscle protein synthesis (Rieu et al., 2006), which is a nutrient signaling molecule in the mTOR pathway (Nie et al., 2018). Dietary supplementation with 0.35% L-leucine in intrauterine growth-restricted (IUGR) piglets decreased the cortisol level in serum and stimulated hepatic protein anabolism via activating mTOR phosphorylation (Zhang et al., 2022a). After infection with porcine rotavirus, supplementation with 1% leucine promoted mucin production and goblet cell numbers in jejunal mucosa, and ameliorated diarrhea in weaned piglets (Mao et al., 2015). In growing pigs constantly exposed to heat stress, dietary supplementation with 0.5% leucine significantly increased average daily gain and reduced backfat thickness (Yin et al., 2022).

2.2. Low protein diet

In invertebrate models, rodents and non-human primates, reducing dietary crude protein (CP) extensively regulates gut microbiota composition and alleviates stress by inactivating nutrient-signaling pathways, including the target-of-rapamycin

Table 1
Summary of studies about the application of functional amino acids in stress-resistance of swine.

Compound	Pig	Dose	Stress type	Effect	Reference
Arg	Sows	33–36 g/d	Oxidative stress	↑: The concentrations of Arg and ornithine (sow blood), the alive litter weight at birth and survival (newborn piglets)	Hong et al. (2020)
Arg	Weaning piglets	0.4%	Heat stress	↑: Average daily gain, feed efficiency	Yun et al. (2020)
Arg	Boars	0.8% or 1.0%	Heat stress	↑: Sperm motility, total sperm number, GSH, the activity of GPx and CAT (seminal plasma) ↓: MDA (sperm)	Chen et al. (2018b)
Arg	Weaned piglets	1.6%	Oxidative stress	↑: The activity of GPx and SOD (plasma) ↓: IL-6 and TNF-α mRNA (liver)	Zheng et al. (2013)
Arg, Lys	Finishing pigs	2%	Transportation stress	↑: Urea production (plasma) ↓: Cortisol (plasma)	Srinongkote et al. (2003)
Glu, Asp	Weaned piglets	2% and 1%, respectively	Oxidative stress	↓: MDA (serum)	Duan et al. (2016)
Glu	Piglets	2%	Oxidative stress	↑: body weight, feed intake, SOD (serum) ↓: MDA (serum)	Yin et al. (2015b)
Glu	Boars	2%	Oxidative stress	↑: the mRNA expression of CAT, Cu/Zn-SOD and GPx4 (testis & epididymis), spermatogonium integrity, sperm count, SOD (testis) ↓: MDA (testis)	Tang et al. (2020)
Glu	Weaned piglets	2%	Oxidative stress	↑: Intestinal intraepithelial lymphocyte number, GSH (jejunum) ↓: Mast cell number, MDA (jejunum), cortisol (serum)	Guo et al. (2022)
Monosodium glutamate	Post-weaning pigs	4%	Weaning stress	↑: Daily weight gain, feed efficiency, Glu concentration (plasma) ↓: Diarrhea incidence	Rezaei et al. (2013)
Leu	Intrauterine growth-restricted piglets	0.35%	Oxidative stress	↑: Alkaline phosphatase activity (serum), protein anabolism (hepatic) ↓: Cortisol (serum)	Zhang et al. (2022a)
Leu	Weaned piglets	1%	Immune stress	↑: Mucin production, goblet cell number (jejunal mucosa) ↓: Diarrhea	Mao et al. (2015)
Leu	Growing pigs	0.5%	Heat stress	↑: Average daily gain, the ratio of feed intake to body weight gain ↓: Backfat thickness	Yin et al. (2022)
Asp	Weanling piglets	1%	Immune stress	↑: ATP, ADP, TAN, AEC, citrate synthase activity, isocitrate dehydrogenase, α-oxoglutarate dehydrogenase complex (jejunum & ileum) ↓: AMP/ATP ratio, AMPKα1 mRNA, SIRT1 mRNA, PGC-1α mRNA (jejunum), pAMPKα/tAMPKα ratio (ileum)	Pi et al. (2014)
Met	Nursery pigs	0.145%	Oxidative stress	↑: GSH (duodenum), TAC (duodenum mucosa & liver) ↓: MDA (plasma)	Shen et al. (2014)
Met	Intrauterine growth-restricted piglets	5.2 g/kg	Oxidative stress	↑: Villus height, GSH, GSH/GSSG ratio, OCLN protein expression (jejunum) ↓: MDA, protein carbonyl, apoptosis index (jejunum)	Su et al. (2018)

AEC = adenylate energy charge; AMPK = AMP-activated protein kinase; CAT = catalase; GPx = glutathione peroxidase; GSH = glutathione; GSSG = oxidized glutathione; IL = interleukin; MDA = malondialdehyde; OCLN = occludin; pAMPKα = phosphorylated AMPKα; PGC-1α = peroxisome proliferator-activated receptor-γ co-activator-1α; SIRT = silent information regulator; SOD = superoxide dismutase; TAC = total antioxidant capacity; tAMPKα = total AMPKα; TAN = total adenine nucleotide; TNF = tumor necrosis factor.

pathway, insulin-like growth factor-1, and mTOR/S6K1 pathway (Mirzaei et al., 2016; Fan et al., 2017). In antibiotic-free diets, a low protein diet is expected to improve pig health and breeding environment, under the premise that the requirements for essential amino acids and total nitrogen, according to the standard recommended by the NRC, are met (Gloaguen et al., 2014; Wessels et al., 2016). It was reported that each 1% reduction in dietary CP decreased the percentage of dietary protein ingredients by 3% (Wang et al., 2018b) (Table 2).

Weaning stress in piglets manifests as bacterial infection, intestinal impairment and frequent diarrhea (Pluske et al., 2002; Campbell et al., 2013; Wen et al., 2018). Foods with high protein were reported to reduce pepsin activity and acid hydrolysis that hinders food breakdown and gastric emptying (Mennah-Govela et al., 2020). Diarrhea in piglets fed high protein diets is related to undigested protein in the intestine (Gao et al., 2022). With excessive protein fermentation, colonic microbes produce toxic metabolites, such as ammonia, sulfides and indoles (Windey et al., 2012; Rist et al., 2013). Without additional antibiotics, reducing dietary CP level from 24.3% to 17.3%, could significantly decrease the abundance of *Escherichia coli* (*E. coli*) in feces in weaned piglets (Heo et al., 2008). Reducing the dietary CP level of weaned piglets to 17% and adding 0.13% isoleucine were found to markedly decrease diarrhea rate, as well as nitrogen excretion (Lordelo et al., 2008). After 2 weeks of a low protein diet, the levels of ammonia-N, histamine and putrescine were decreased in colonic digesta (Wen et al., 2018).

Environmentally-induced hyperthermia compromises nutrient intake in growing pigs (Pearce et al., 2010). Circulating stress hormones are elevated in response to environmental heat, including epinephrine, glucagon, and cortisol (Rhoads et al., 2013). In the gastrointestinal tract, increased vasoconstriction redistributes blood to the periphery and relieves heat stress (Hales et al., 1979; Lambert, 2009). However, the redirection of blood flow under heat stress could decrease the supply of oxygen and nutrients to the small intestine, resulting in high mortality and morbidity (Liu et al., 2009; Baumgard et al., 2013; Ross et al., 2015). One strategy to alleviate heat stress is to decrease dietary protein level, which mildly induces defense mechanisms (Quiniou et al., 2000; Sinclair, 2005). For growing pigs under heat stress, Morales et al. reduced dietary CP levels to 13.5% and supplemented with lysine, threonine, methionine, tryptophan, histidine, isoleucine, leucine,

Table 2
Summary of studies about the application of a low protein diet in stress-resistance of swine.

Crude protein	Pig	Breed	Stress type	Effect	Reference
17.25%	Weaned piglets	Large × White × Landrace	Oxidative stress	↑: The expression of mitochondrial succinate dehydrogenase complex subunit A, phosphoglycerate kinase 1, functional epoxide hydrolase and alternative pig liver esterase (jejunum) ↓: HSP60 (jejunum)	Ren et al. (2014a)
18%	Weaned piglets	Yorkshire × Landrace	Oxidative stress	↑: *Parabacteroides*, *Bacteroides* (colon), mixed neutral-acidic mucins, the OCLN mRNA expression (colon) ↓: *Desulfovibrio*, *Clostridium*, *Ruminococcus* (colon)	Li et al. (2019b)
13.5%	Growing pigs	Landrace × Hampshire × Duroc	Heat stress	↑: Absorption capacity (small intestine), villi height: crypt depth ratio (duodenum &jejunum) ↓: Amino acids transporter B^{+0} (ileum)	Morales et al. (2020)
14%	Sows	Yorkshire × Landrace	Heat stress	↓: Body temperature, respiration rate	Zhang et al. (2020a)
17.3%	Weaned piglets	Large White × Landrace	Weaning stress	↓: Diarrhea rate, *E. coli* (feces)	Heo et al. (2008)
17%	Weaned piglets	Landrace × Duroc	Weaning stress	↓: Nitrogen intake, nitrogen excretion	Lordelo et al. (2008)
17%	Weaned piglets	Duroc × Landrace × Large White	Weaning stress	↓: Diarrhea rate, the levels of ammonia nitrogen, histamine and putrescine (colonic digesta)	Wen et al. (2018)
12%	Sows	Purebred Huzhu bamei pigs	Weaning stress	↑: litter sizes (sows), Fusobacteria, Actinobacteria (piglet jejunum) ↓: Firmicutes (piglet jejunum), diarrhea rate (piglets)	Jin et al. (2019)

HSP = heat shock protein; OCLN = occludin.

phenylalanine, and valine, which increased the absorption capacity of the small intestine and mitigated intestinal damage (Morales et al., 2020). When dietary CP levels of sows were decreased from 19.3% to 14%, with a balanced diet that achieved a near ideal amino acid profile throughout lactation, this relieved high body temperatures experienced by sows under heat stress (Zhang et al., 2020a).

2.3. Plant extracts

Plant extracts are complex mixtures purified from natural compounds containing essential oils, polyphenols, flavonoids, polysaccharides, and lectin (Armendariz-Barragan et al., 2016; Liu et al., 2018b). Thymol, carvacrol, and eugenol are able to down-regulate the gene expression of bacterial virulence factors, quorum sensing, and biofilm formation, which demonstrates their ability to control enterotoxigenic *E. coli* (ETEC) infection (Bonetti et al., 2020). Paeoniflorin and essential oil was found to disrupt quorum sensing of bacteria, reducing virulence of *Streptococcus suis* (Li et al., 2021a) and ETEC (Choi et al., 2020). With antioxidant (Clark. 1996; Liu et al., 2018b), antiviral (Surya et al., 2014), antifungal (Chakraborty et al., 2014) and antiparasitic (Lemuh et al., 2015) properties, plant extracts alleviate the stress response in swine through various mechanisms (Hao et al., 2021), including via the PI3K/AKT/mTOR (Zhang et al., 2019a; Radwan et al., 2020), Keap1-Nrf2 (Meng et al., 2018) and NF-κB pathways (Zou et al., 2016) (Table 3).

When a sow is pregnant or parturient, free radicals are often generated in the placenta and newborn piglet due to changes in the environment (Myatt et al., 2004; Jain, 2016). In gestating gilts, supplementing silymarin at 8 g/d elevated prolactin concentration, inducing an increase in SOD activity, protecting sows against oxidative stress (Farmer et al., 2016). Dietary curcumin supplementation at 400 mg/kg increased antioxidant capacity in IUGR piglets through upregulating Nrf2 and Hmox1 levels in livers (Niu et al., 2019).

Weaning stress is often accompanied by intestinal, microbial and immunological changes, causing diarrhea and other diseases (Fairbrother et al., 2005; Chen et al., 2015). In weaning piglets, dietary supplementation with *Eucommia ulmoides* leaf extract was shown to improve growth performance and jejunal morphology with a concurrent reduction in diarrhea rate (Peng et al., 2019). Grape seed proanthocyanidins at 250 mg/kg alleviated intestinal oxidative stress and diarrhea by decreasing intestinal permeability and improving intestinal morphology (Han et al., 2016). Paper mulberry leaf extract at 150 or 300 g/t, significantly increased the level of GPx, catalase (CAT), SOD and Ig, and reduced the diarrhea rate, improving antioxidant capacity and immune function (Chen et al., 2020a).

During transportation, pigs suffer the inevitable physical and psychological challenges from noise, motion, fasting, dehydration, crowding and temperature variation (Tarrant, 1989; Peeters et al., 2004). Several plant extracts have shown ability to alleviate the negative effects of transportation stress (Zou et al., 2016). Before transportation, supplementation of quercetin at 25 mg/kg in finishing pig diets reduced intestinal injury via decreasing intestinal ROS level and inactivating the ERK1/2, JNK, AKT and NF-κB signaling pathways (Zou et al., 2016). Oregano essential oil is an aromatic plant extract (Vokou et al., 1993) with carvacrol and thymol (Sivropoulou et al., 1996). To mitigate transportation stress, supplementing oregano essential oil at 25 mg/kg in finishing pigs reduced MDA level and increased SOD activity in liver (Zhang et al., 2015).

In swine production, environmental temperature shock could cause heat stress or cold stress (Hao et al., 2021; Yang et al., 2021c). Currently, there are few studies on the use of plant extracts to alleviate cold stress in swine, which are mostly in poultry (Hu et al., 2021). When muscle cells are exposed to heat stress, gintonin-enriched fraction, a non-saponin ingredient in ginseng, could inhibit the inflammatory response through the NLRP3 inflammasome and LPA receptor (Chei et al., 2020). As an organic osmolyte, betaine is known to counteract harmful effects of heat stress by reducing basal metabolic rate and the activity of membrane-bound ATPases (Moeckel et al., 2002; Shadmehr et al., 2018; Li et al., 2019a). Supplementation of 1 g/kg betaine in the diet of female grower pigs prevented high rectal temperatures and the increase in colon permeability caused by heat stress (Le et al., 2020).

2.4. Organic acids

Young weaned piglets have a low appetite and insufficient production of digestive enzymes (Suiryanrayna et al., 2015). Organic acids confer good digestive capacity and high feed conversion rate allowing piglets to transition from milk to solid feed by lowering pH value (Canibe et al., 2003, 2007). Organic acids are characterized by reducing pathogen colonization and increasing

Table 3
Summary of studies about the application of plant extracts in stress-resistance of swine.

Plant extracts	Pig	Dose	Stress type	Effect	Reference
Silymarin	Gestating gilts	4 g/d	Oxidative stress	↑: Prolactin circulating concentrations (liver & plasma) ↓: Protein carbonyls (liver)	Farmer et al. (2016)
Dioscin	Growing pigs	80 mg/kg	Oxidative stress	↑: Sirt1 protein, Nrf2 protein, LVEF, SOD, CAT, GSH (serum) ↓: CK, CK-MB, LDH, cTnT (serum), p-p38 MAPK protein expression, MDA, TNF-α, IL-1β, IL-6, IL-18 (serum)	Yang et al. (2018a)
Resveratrol	Weaned piglets	100 mg/kg	Oxidative stress	↑: Mitochondrial DNA, T-AOC (jejunum) ↓: ROS, H_2O_2, MDA (jejunum)	Cao et al. (2019)
Curcumin	Intrauterine growth retardation neonatal piglets	400 mg/kg	Oxidative stress	↑: Body-weight gain, feed intake, CAT, T-AOC (serum), Nrf2, Hmox1 (liver) ↓: MDA, AST, ALT (serum)	Niu et al. (2019)
Icariin	Newborn piglets	1 g/kg	Immune stress	↑: average daily gain, ZO-1, OCLN (jejunum), SOD, GPx, CAT, T-AOC (jejunum) ↓: Diarrhea rate, IL-1β, IL-6, IL-8, TNF-α (jejunum), ROS, RNS, MDA, H_2O_2, p38 MAPK (jejunum)	Xiong et al. (2020)
Oregano essential oil	Finishing pigs	25 mg/kg	Transportation stress	↑: ROS, MDA, GPx, SOD (serum), HSP27, HSP90 (liver) ↓: Norepinephrine concentrations, cortisol (serum)	Zhang et al. (2015)
Quercetin	Finishing pigs	25 mg/kg	Transportation stress	↑: OCLN, ZO-1 mRNA expression, villi height (jejunum) ↓: ROS, MDA, endotoxin, TNF-α, IL-1β, IL-6, MCP-1 (jejunum), NF-κB-p65 protein, phosphorylated Akt protein (jejunum)	Zou et al. (2016)
Betaine	Growing pigs	1 g/kg	Heat stress	↑: IL-1β, total antioxidant capacity (plasma)	Le et al. (2020)
Betaine	Growing-finishing pigs	0.1%	Heat stress	↓: Epinephrine (serum)	Lan et al. (2018)
Capsicum oleoresin	Gilts and barrows	0.1 g/kg	Heat stress	↑: Basophil count ↓: Circulating glucose concentrations	Biggs et al. (2020)
Grape seed proanthocyanidins	Weaned piglets	250 mg/kg	Weaning stress	↑: Villus height: crypt depth, villus height, propionic acid, butyric acid, Clostridiaceae (ileum & colon) ↓: Diarrhea incidence, Lactobacillaceae (ileum & colon)	Han et al. (2016)
Eucommia ulmoides leaf extract	Weanling piglets	0.5%	Weaning stress	↑: Firmicutes, acetate, villus height: crypt depth, claudin-3 mRNA (jejunum) ↓: Diarrhea rate, crypt depth, Bacteroidetes (colon)	Peng et al. (2019)

Akt = protein kinase B; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAT = catalase; CK = creatine kinase; cTnT = cardiac troponin T; GPx = glutathione peroxidase; GSH = glutathione; H_2O_2 = hydrogen peroxide; HO1 = heme oxygenase 1; HSP = heat shock protein; IL = interleukin; Keap1 = Kelch-like epichlorohydrin-associated protein 1; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MAPK = mitogen-activated protein kinase; MCP = monocyte chemotactic protein; MDA = malondialdehyde; NF-κB-p65 = nuclear factor kappa B-p65; Nrf2 = nuclear factor erythroid 2-related factor 2; OCLN = occludin; RNS = reactive nitrogen species; ROS = reactive oxygen species; Sirt1 = sirtuin1; SOD = superoxide dismutase; T-AOC = total antioxidant capacity; TNF = tumor necrosis factor; ZO-1 = zonula occudens-1.

appetite in pigs, and have been safely added to animal feed as growth promoters for over five decades (Partanen et al., 1999; Ferronato et al., 2020). In particular, some organic acids function as energy sources as they are intermediary products in the tricarboxylic acid cycle (Giesting et al., 1985) (Table 4).

2.4.1. Short chain fatty acids

Short chain fatty acids (SCFAs) are a subset of saturated fatty acids with six or less carbon molecules (Tan et al., 2014). Acetate, propionate and butyrate play a beneficial role in inflammation (Ren et al., 2019), gut integrity (Diao et al., 2019), and antioxidant capacity (Rosignoli et al., 2001). The concentration of SCFAs is the highest in the proximal colon, where they are rapidly absorbed into colonocytes or through the portal vein into the liver or systemic circulation. The absorbed SCFAs participate in de novo synthesis of lipid and glucose through fatty acid oxidation, which can regulate energy homeostasis (Wolever et al., 1989). In newborn piglets, oral administration of 500 mg/day butyrate significantly enhanced post-weaning body weight by 13% (Lu et al., 2012). After ETEC challenge, a mixture of formic acid and propionic acid at 1% in weaning piglets was regarded as a valid alternative to antibiotics, which reduced inflammatory response and diarrhea incidence (Ren et al., 2019). Gastric infusion of high dose SCFAs increased the villus height and SOD activity in the jejunum of weaning piglets (Diao et al., 2019). Interestingly, butyrate also serves as a signaling molecule to mediate intestinal barrier function and LPS-induced inflammation via activating GPR41, GPR43 and GPR109a (He et al., 2020; Zhang et al., 2021). In IPEC induced by H_2O_2, sodium butyrate at 1 mmol/L induced mitophagy by activating AMPK and alleviated intestinal epithelium barrier injury (Li et al., 2022). Supplementation with 1,000 mg/kg sodium butyrate in the diet decreased the levels of TNF-α and interleukin-6 in serum and inhibited the DNA-binding activity of intestinal NF-κB in weaned piglets (Wen et al., 2012).

2.4.2. Medium chain fatty acids

Among medium chain fatty acids (MCFA), caprylic acid (C8:0), capric acid (C10:0), and lauric acid (C12:0) are most the common in nature. These saturated 7 to 12 carbonic acids are abundant in milk from rats, rabbits, sows and humans (Decuypere et al., 2003; Tvrzicka et al., 2011; Gardner et al., 2017; Hu et al., 2019). MCFA possess the ability to improve feed digestibility and growth performance (Baltić et al., 2017). Encapsulation in a carrier is a strategy to efficiently guide free MCFA delivery to the target regions of the gastrointestinal tract (Jackman et al., 2020). Hydrolysis of medium-chain triglycerides (MCT) can produce MCFA (Ferronato et al., 2020). One of the advantages of MCT is that they overcome the repellent odor and the volatility of free acids during feeding (Decuypere et al., 2003). Compared with long-chain triglycerides, MCT provides higher satiety and longer gastric emptying times (St-Onge et al., 2002; Maher et al., 2019). Dietary MCT supplementation (920 g/kg C8, 20 g/kg C10, and 60 g/kg C12) for sows significantly improved the survival of offspring, especially for newborn piglets with low birth weight (Jean et al., 1999). Dietary supplementation of 7.75 g/kg MCFA (70% MCT) increased the concentrations of IgA, IgG and IgM in colostrum and decreased diarrhea incidence in suckling piglets (Chen et al., 2019a).

Table 4
Summary of studies about the application of organic acid in stress-resistance of swine.

Compound	Pig	Dose	Stress type	Effect	Reference
Short-chain fatty acid mixture	Neonatal germ-free piglets	25 mL/kg	Oxidative stress	↑: G-protein-coupled receptor-43 mRNA, glucagon-like peptide-2, white blood cell, neutrophils, lymphocyte (blood) ↓: The mRNA expression of IL-1β (jejunum & ileum), the mRNA expression of IL-6 (colon)	Zhou et al. (2020a)
Sodium butyrate	Neonatal piglets	150 mmol/L	Oxidative stress	↓: The gene expressions of IL-6, IL-8, IFN-γ, IL-10, IL-1β, TGF-β (ileum)	Xu et al. (2016)
Sodium butyrate	Growing-finishing pigs	0.2%	Oxidative stress	↑: Final body weight, daily body weight gain, daily feed intake, carcass weight, Bacteroidetes (cecum) ↓: Proteobacteria (cecum)	Sun et al. (2020b)
Sodium butyrate	Weaned piglets	1,000 mg/kg	Immune stress	↑: Clostridiaceae, Ruminococcaceae, Lachnospiraceae, Bacteroidete (ileal & colonic lumen) ↓: Diarrhea incidence, TNF-α (serum), MDA (serum)	Huang et al. (2015)
Medium chain fatty acids	Sows	7.75 g/kg	Immune stress	↑: The concentrations of IgA, IgG and IgM (sow colostrum) ↓: The incidence of diarrhea (suckling piglets)	Chen et al. (2019a)
Medium chain fatty acid salts	Piglets	No data	Immune stress	↓: The intestinal colonization of *Salmonella* or *E. coli*	Lopez-Colom et al. (2019)
Medium chain fatty acid calcium soap	Growing pigs	No data	Immune stress	↓: The abundances of *E. coli* and *Campylobacter* (feces)	Matsui et al. (2021)
Lactic acid	Sows	2.8%	Immune stress	↓: *Salmonella* Typhimurium counts (feces)	Tanaka et al. (2010)
Alpha-ketoglutaric acid	Growing pigs	1%	Oxidative stress	↑: AEC (jejunal mucosa & ileal mucosa), the oxidation of glucose, Gln and oleic acid (enterocytes) ↓: AMP: ATP ratio (jejunal mucosa & ileal mucosa)	Hou et al. (2011b)
Alpha-ketoglutaric acid	Growing pigs	1%	Oxidative stress	↑: Glu, Gln, Leu, Asn, Lys, Ala, Ser, Thr, Val, Phe (liver), GPx activity (liver), ADP (liver) ↓: AST activity, AST/ALT ratio, Glu (plasma), MDA, total protein (liver)	Wang et al. (2015)
Chlorogenic acid	Weaned piglets	1,000 mg/kg	Oxidative stress	↑: The activity of SOD, GPx and CAT (serum)	Zhang et al. (2018)
Benzoic acid	Growing pigs	5,000 mg/kg	Oxidative stress	↑: The activity of SOD and GPx (jejunal mucosa)	Diao et al. (2016)

AEC = adenylate energy charges; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAT = catalase; GPx = glutathione peroxidase; Ig = immunoglobulin; IL = interleukin; MDA = malondialdehyde; SOD = superoxide dismutase; TGF = transforming growth factor; TNF = tumor necrosis factor.

Capric acid and lauric acid have exhibited abilities to inhibit pathogens (Yoon et al., 2018). The antibacterial properties of MCFA depend on disrupting the phospholipid membrane surrounding membrane-enclosed pathogens to induce bacterial cell lysis in the gastrointestinal tract (Yoon et al., 2018; Lauridsen, 2020). In early-life piglets, a mixture of MCFA salts, to some extent, reduced negative effects of *Salmonella* and ETEC K88, which regulate the local immune cell response at the ileal level (Lopez-Colom et al., 2019). In growing pigs, dietary supplementation with MCFA calcium soap significantly decreased the abundance of *E. coli* and *Campylobacter jejuni* in feces (Matsui et al., 2021).

2.4.3. Lactic acid

Lactic acid is synthesized as an end product of sugar fermentation in the stomach and small intestine, and it is the most widely distributed hydroxycarboxylic acid in nature (Partanen et al., 1999; Sun et al., 2020a). It is involved in redox reactions and hydroxyl substitutions (Joshi et al., 2010). Lactic acid exerts a certain antibacterial effect by lowering gastric pH and stimulating pancreatic exocrine response (Suiryanrayna et al., 2015; Ferronato et al., 2020). In piglets, dietary supplementation with 2.8% lactic acid suppressed *Salmonella* Typhimurium content in feces, and ameliorated diarrhea (Tanaka et al., 2010).

2.4.4. Alpha-Ketoglutarate

Alpha-Ketoglutarate (AKG) is involved in amino acid metabolism to maintain ATP homeostasis and the balance between nitrogen and ammonia (Hou et al., 2011a; Bayliak et al., 2021; Gyanwali et al., 2022). In LPS-challenged growing pigs, supplementation with 1% AKG decreased the AMP:ATP ratio in intestinal mucosa (Hou et al., 2011b). In weaned piglets with LPS challenge, supplementation with 1% AKG also alleviated histomorphological abnormalities and increased GPx activity in the liver (Wang et al., 2015). Further, AKG supplementation alleviated mucosal damage by increasing the concentration of heat shock protein 70 and the ratio of p-mTOR to mTOR in the jejunum (Hou et al., 2010).

2.4.5. Chlorogenic acid

Chlorogenic acid (5-*O*-caffeoylquinic acid, CGA) is an organic acid which is widely distributed in tea and coffee (Hayakawa et al., 2020). The beneficial properties of dietary CGA have been evidenced through various animal models and clinical studies (Santana-Gálvez et al., 2017; Chen et al., 2018a; Hayakawa et al., 2020). The antioxidant activity of CGA prevented H_2O_2-induced ROS generation in rats (Zhou et al., 2016). In mice, CGA may alleviate indomethacin-induced inflammation and mucosal injury via suppressing the growth of *Bacteroides* (Yan et al., 2020). In weaned piglets, dietary supplementation with 0.1% CGA increased the activity of SOD, GPx and CAT in serum. It also selectively increased the population of *Lactobacillus* and decreased the population of *E. coli* in the colon (Zhang et al., 2018).

2.4.6. Benzoic acid

Benzoic acid is the simplest aromatic carboxylic acid (Ferronato et al., 2020) and is used as a fragrance ingredient and preservative (Johnson et al., 2017). Though controversial effects and unclear mechanisms, benzoic acid, in appropriate concentrations, has been reported to improve growth performance partly via regulating redox status (Del Olmo et al., 2017; Johnson et al., 2017; Mao et al., 2019; Ferronato et al., 2020). Adding 0.5% benzoic acid to the basal diet of growing pigs increased the activity of GPx and SOD in the jejunal mucosa (Diao et al., 2016).

2.5. Prebiotics

Derived from nonviable food components (Pineiro et al., 2008), prebiotics with different molecular structures participate in the modulation of bacterial composition in the large intestine (Gaggia et al., 2010). At present, the most widely used prebiotics are fructo-oligosaccharides (FOS) (Singh et al., 2017; Mao et al., 2018; Schokker et al., 2018), chito-oligosaccharides (COS) (Zivanovic et al., 2007), mannan-oligosaccharides (MOS) (Yazbeck et al., 2019), non-starch polysaccharides (NSP) (Chen et al., 2021b), γ-aminobutyric acid (GABA) (Xia et al., 2019), microalgae and seaweeds (Gaggia et al., 2010; de Jesus Raposo et al., 2016; Corino et al., 2019), all of which possess antioxidant and antibacterial properties (Table 5).

2.5.1. Fructo-oligosaccharides

FOS are soluble dietary fibers with D-fructose linked by β-(2,1) bonds (Gibson et al., 1995; Roberfroid et al., 2010). FOS are beneficial to gut barrier function and immunological function in swine (Gao et al., 2001; Csernus et al., 2020). During immune stress induced by ETEC, supplementation with FOS at 2.5 mg/kg decreased interleukin-1β and TNF-α, and increased jejunal immunoglobulins (Liu et al., 2020). In diarrheal weanling piglets, a diet containing 1% FOS improved expression of Nrf2 and reduced diarrhea incidence (Zhang et al., 2022c).

Constipation heavily impairs the reproductive performance of sows and exacerbates the oxidative stress in parturition (Oliviero et al., 2010; Zhang et al., 2017; Yu et al., 2021), accompanied by mastitis (Peltoniemi et al., 2016) and udder infection (Oliviero et al., 2010). Supplementation with 1.5% FOS alleviated constipation and enhanced the antioxidant defense capacity of sows via increasing the activity of total SOD and GPx and decreasing the serum MDA concentration (Wang et al., 2016).

2.5.2. Chito-oligosaccharides

COS are chemically and enzymatically hydrolyzed from chitosan, and have the characteristics of low molecular weight, good solubility, and low viscosity (Chae et al., 2005). Compared to 2 or 3 kDa, COS with molecular weight 5.1 kDa exhibited the highest radical scavenging activity (Yang et al., 2017). COS could also be added to the animal diet as a biological or pharmaceutical excipient to promote growth performance through enhancing immunity status and modulating gut microbiota and intestinal morphology in weaned piglets (Singla et al., 2001; Yang et al., 2012; Zhao et al., 2017). To cope with oxidative stress in the placenta, COS supplementation at 0.03‰ in the pregnant sow's diet significantly increased total SOD activity in plasma during late gestation (Xie et al., 2016). In ETEC-challenged pigs, COS supplementation at 300 mg/kg improved the mRNA expressions of interleukin-1β and interleukin-6 in the jejunal mucosa (Xiao et al., 2014). For weaning stress, COS supplementation at 100 or 200 mg/kg could increase the abundance of *Lactobacillus* in feces and enhance villus height to decrease diarrhea incidence (Liu et al., 2008).

2.5.3. Mannan-oligosaccharides

Yeast is the most common commercial source of MOS, whose supplementation results in high feed conversion and enhanced Ig concentrations (Tizard et al., 1989; LeMieux et al., 2003; Bland et al., 2004). In sows during pregnancy and lactation, supplemental MOS improved the immune competence and growth performance in offspring. The MOS supplementation at 400 mg/kg in sows increased SIgA content in jejunal mucosa of piglets, downregulated the expressional levels of TLR2, TLR4, and interleukin-8 in intestinal mesenteric lymph and decreased interleukin-2 and interleukin-4 concentrations in serum of piglets (Duan et al., 2019a).

The type of glycosidic linkage and proportion of mannose in yeast products determine the ability of MOS to bind to or

Table 5
Summary of studies about the application of prebiotics in anti-stress of swine.

Prebiotic	Pig	Dose	Stress type	Effect	Reference
FOS	Weaned piglets	2.5 mg/kg	Immune stress	↑: *Bacillus*, *Bifidobacterium* (cecum), IgA, IgM, SIgA (jejunum) ↓: IL-1β, TNF-α (plasma), *E. coli* (cecum), IL-6 mRNA (jejunum & ileum), IL-1β mRNA (duodenum), TNF-α mRNA (jejunum & ileum & duodenum)	Liu et al. (2020)
FOS	Weanling piglets	1%	Oxidative stress	↑: *Sharpea*, *Megasphaera*, *Bacillus* (ileum), Nrf2 (serum) ↓: D-lactate, TNF-α (serum)	Zhang et al. (2022c)
FOS	Weaning piglets	5 g/kg	Immune stress	↑: Average daily gain, IgG (serum)	Wang et al. (2019b)
COS	Weaning piglets	158.8 mg/kg	Weaning stress	↑: *Lactobacillus* (fecal samples), villus height (ileum) ↓: *E. coli* (fecal samples)	Liu et al. (2008)
COS	Sows	30 mg/kg	Oxidative stress	↑: SOD (plasma), Cu/Zn-SOD mRNA, CAT mRNA (placenta) ↓: D-lactate, TNF-α, MDA (plasma), IL-6, IL-8 (placenta)	Xie et al. (2016)
GABA	Weaned piglets	20 mg/kg	Immune stress	↑: IFN-γ, IL-4, IL-10, TLR6 (ileum) ↓: IL-22, IL-1, IL-18, MUC1 (ileum)	Chen et al. (2019b)
GABA	Growing-finishing pigs	30 mg/kg	Transportation stress	↓: MDA, adrenal cortical hormone, cortisol (serum)	Bi et al. (2020)
GABA	Growing-finishing pigs	20 mg/kg	Oxidative stress	↓: TLR4/NF-κB ↑: PPARγ mRNA, GABARs mRNA, TNF-α, IL-1β (liver)	Zhang et al. (2022b)
Inulin	Piglets	4%	Immune stress	↑: SCFA (colon), *Bifidobacteria*, *Lactobacilli* (cecum)	Tako et al. (2008)
Microalgae	Pregnant sows	3.12%	Oxidative stress	↑: Total omega-3 polyunsaturated fatty acids, docosahexaenoic acid (plasma)	You et al. (2019)
MOS	Weaned piglets	0.1%	Oxidative stress	↑: IgG (serum)	Li et al. (2021b)
MOS	Sows	8 g/d	Oxidative stress	↑: IgG (sow colostrum and plasma & suckling piglet serum)	Czech et al. (2010)
MOS	Sows; piglets	400 mg/kg; 800 mg/kg	Oxidative stress	↑: NF-κB p65 mRNA (sow jejunum), *Lactobacillus* (piglet jejunum & ileum), SIgA (piglet jejunum), IL-10 (piglet serum) ↓: IL-2 (sow intestinal lymphatic), IL-4 (sow intestinal lymphatic), *E. coli* (piglet jejunum & cecum), TLR2 mRNA (piglet jejunum), TLR4 mRNA (piglet jejunum), IL-8 mRNA (piglet jejunum)	Duan et al. (2019a)

CAT = catalase; COS = chito-oligosaccharide; FOS = fructo-oligosaccharide; GABA = gamma-aminobutyric acid; GABARs = gamma-aminobutyric acid receptors; Ig = immunoglobulin; IL = interleukin; MDA = malondialdehyde; MOS = mannan-oligosaccharides; MUC = mucin; NF-κB = nuclear factor-kappa B; Nrf2 = nuclear factor erythroid 2-related factor 2; PPARγ = peroxisome proliferator-activated receptor γ; SCFA = short chain fatty acids; SIgA = secretory immunoglobulin A; SOD = superoxide dismutase; TLR = toll-like receptor; TNF = tumor necrosis factor.

agglutinate bacteria including *E. coli* (Singboottra, 2005; Pourabedin et al., 2014). In *E. coli* LPS-challenged weanling pigs, MOS supplementation at 0.1% was found to increase circulating IgG concentration (Li et al., 2021b). Besides, MOS in weanling piglets enhanced resistance to the porcine reproductive and respiratory syndrome (PRRS) virus (Che et al., 2011) and Aujeszky's disease (Nochta et al., 2009). During the early infection stage of PRRS in weaned piglets, MOS supplementation at 0.2% increased concentrations of interleukin-10 and white blood cells (Che et al., 2011).

2.5.4. Non-starch polysaccharides

NSPs consist of a soluble fraction with pectin, some hemicellulose and oligosaccharides, and a non-soluble fraction with cellulose and hemicellulose (Bakker et al., 1998). Due to the low cost, low toxicity (Jiang et al., 2019; Zhang et al., 2019b) and antioxidant activity (Chen et al., 2021b), water-soluble non-starch polysaccharides from natural resources have drawn attention in animal husbandry. NSP isolated from *Sarcodon aspratus* activates the NF-κB and MAPK pathways and promotes pinocytic activity of macrophages (Wang et al., 2018a). In a dextran sodium sulfate-challenged pig model, supplementation with algal polysaccharides laminarin and fucoidan reduced interleukin-6 mRNA abundance in the colon, which alleviated diarrheal symptoms (O'Shea et al., 2016).

2.5.5. Gamma-aminobutyric acid

As the most important inhibiting neurotransmitter in the brain (Sarkar et al., 2016), GABA plays a role in regulation of apoptosis (Wang et al., 2018c), intracellular autophagy (Hui et al., 2019) and inflammation (Dias et al., 2014). In ETEC-infected IPEC-J2, GABA at 20 mg/kg activated $GABA_A$ receptor signaling and the AMPK-autophagy pathway to attenuate ETEC-induced apoptosis (Xia et al., 2019). In growing-finishing piglets, supplementation with GABA at 20 mg/kg was found to promote feed conversion and decrease TLR4/NF-κB signaling by acting on GABA receptors (Zhang et al., 2022b). GABA can be produced from *Lactobacillus* and *Bifidobacterium* (Barrett et al., 2012). In ETEC-challenged piglets, GABA supplementation markedly regulated the serum amino acid profile and enhanced the community richness and diversity in the ileal microbiome (Chen et al., 2020c).

2.5.6. Microalgae and seaweeds

Microalgae and seaweeds show positive effects on growth of beneficial bacteria in the gut (de Jesus Raposo et al., 2016; Corino et al., 2019). They are a variety of carboxylated and sulfated polysaccharides, like alginates, fucoidans, carrageenans, exopolysaccharides, phenols, carotenoid fucoxanthins, tannins and phlorotannins (de Jesus Raposo et al., 2016; Jacobsen et al., 2019). Secondary metabolites from *Cyanobacteria* can overcome ultraviolet radiation-deleterious effects (Favas et al., 2022). For LPS challenge in late gestation sows, supplementation with 3.12% microalgae elevated the concentrations of cytokines interleukin-1ra, interleukin-6 and interleukin-10 (Lee et al., 2019). Originating from brown seaweeds, fucoidan is found to alleviate weaning stress via downregulating the abundance of *E. coli* and upregulating the abundance of *Lactobacillus* (Reilly et al., 2008; McDonnell et al., 2010; Walsh et al., 2013).

2.6. Probiotics

In the swine industry, the main probiotics are *Lactobacilli* (Kaizu et al., 1993; Kullisaar et al., 2003), *Bacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* (McCoy et al., 2007; Bajaj et al., 2015). An ideal probiotic is required to have gastric acid resistance and bile salt resistance, intestinal colonization capacity, and the ability to antagonize pathogenic microorganisms (Cho et al., 2011). Splichalova et al. used preterm gnotobiotic piglets as an infectious model at first and verified the safety of *Lactobacillus rhamnosus* GG and its bacterial interference with *Salmonella* Typhimurium (Splichalova et al., 2019). An interesting example is that *Lactobacillus acidophilus* 30SC is a quorum-quenching probiotic bacterium, which inhibits the virulence of enterohemorrhagic *E. coli* by the universal quorum molecule autoinducer-2 in weaning piglets (Kim et al., 2018). Probiotics also work through various mechanisms, such as promoting enzyme activity, secreting secondary metabolites, and activating antioxidant signaling pathways (Wang et al., 2017) (Table 6).

Desirable bacteria not only possess their own antioxidant enzyme systems (Wang et al., 2017), but also regulate the activity of antioxidant enzymes from hosts (Wang et al., 2009). SOD, CAT and GPx are well-known ROS-interacting enzymes (Ho et al., 2004; Landis et al., 2005; Tian et al., 2021). For example, *Lactobacillus fermentum* E−3 (10^7 CFU/mL) and E−18 (10^7 CFU/mL) strains were tolerant to exogenous and endogenous oxidative stresses by expressing Mn-SOD against hydrogen peroxide, superoxide and hydroxyl radicals (Kullisaar et al., 2002). Supplementation of *Bacillus amyloliquefaciens* SC06 at 10^6 CFU/mL or 10^8 CFU/mL elevated glutathione S-transferase and CAT activity in IPEC-1 with H_2O_2-induced oxidative stress (Wang et al., 2017).

Metabolites from probiotics, such as GSH and folate, can regulate the antioxidant capacity in swine (Wang et al., 2017). GSH is the most important low molecular weight antioxidant as it eliminates hydrogen peroxides, hydroxyl radicals, and peroxynitrite (Forman et al., 2009). In a diquat model, the GSH level was increased by supplementation with *L. fermentum* I5007 at 10^8 CFU/mL in weanling piglets. In humans, daily consumption of *L. acidophilus* by children can improve the folate level in plasma (Mohammad et al., 2006), and relieve oxidative stress (Nandi et al., 2005). For weaning stress, supplementation of folate at 9 mg/kg increased the organ weight and stomach pH in piglets (Wang et al., 2021).

Mechanically, it was indicated that probiotics protect hosts against stress through regulating the Nrf2-Keap1 (Wang et al., 2013b), NF-κB (Diao et al., 2014), and MAPK (Tao et al., 2006) pathways in swine (Wang et al., 2017). Recently, *Pediococcus pentosaceus* SMM914 strain at 10^8 CFU/mL isolated from sow milk was found to activate the Nrf2-Keap1 pathway in the liver of weaned piglets (Wang et al., 2022). In piglets, dietary supplementation with *Lactobacillus delbruecki* at 2.01×10^{10} CFU/g activated the TLR-Bruton's tyrosine kinase-Nrf2 signaling pathway and alleviated LPS-induced intestinal oxidative stress (Chen et al., 2021a). Prior to challenge with ETEC K88, *Lactobacillus plantarum* supplementation at 10^8 CFU/well in IPEC-1 was shown to activate the MAPK and NF-κB pathways to inhibit immune stress (Yang et al., 2021a).

2.7. Minerals and vitamins

Apart from these above-mentioned nutritional strategies, there are also other nutritional strategies for mitigating stress, such as minerals and vitamins (Table 7). For minerals, pigs receiving 40 mg/kg Mn, added as $MnSO_4 \cdot H_2O$, showed high average daily gain and feed efficiency (Grummer et al., 1950). Dietary chromium propionate at 200 μg/kg Cr increased blood neutrophils by approximately 37% and had a tendency to increase the average daily feed intake in heat-stressed finishing pigs (Mayorga et al., 2019). Selenoproteins have been identified in both humans and piglets, which mediate the antioxidant and anti-inflammatory functions of Se (Kryukov et al., 2003; Zhang et al., 2011). Supplementation of 1.0 mg/kg Se in gilt diets mitigated increases in rectal temperature and alleviated heat stress in the short-term (Liu et al., 2018a). A high fat diet in uncastrated boars was reported to induce oxidative damage and apoptosis in the liver. Wang et al. (2020a)

Table 6
Summary of studies about the application of probiotics in stress-resistance of swine.

Probiotic	Pig	Dose	Stress type	Effect	Reference
Lactobacillus rhamnosus GG	Preterm gnotobiotic piglets	1×10^8 CFU/mL	Immune stress	↓: IL-8 (serum & jejunum), IL-12/23p40 (jejunum)	Splichalova et al. (2019)
Lactobacillus plantarum strain JDFM LP11	Female crossbred piglets	2.5×10^7 CFU/mL	Immune stress	↑: Firmicutes, Spirochaetes (gut), IgG (serum) ↓: The immune associated BPI, RSAD2, SLPI, LUM, OLFM4, DMBT1 and C6 genes (ileum)	Shin et al. (2019)
Lactobacillus fermentum	Growing-finishing pigs	1×10^9 CFU/mL	Oxidative stress	↑: SOD (serum & muscle), GPx (serum), CAT (liver) ↓: MDA (serum & muscle)	Wang et al. (2009)
Lactobacillus fermentum I5007	Weaned crossbred barrows	1×10^8 CFU/mL	Oxidative stress	↑: SOD and GSH (plasma, muscle & liver) ↓: MDA (muscle & liver)	Wang et al. (2013a)
Saccharomyces boulardii mafic-1701	Weaned piglets	1×10^8 CFU/kg	Oxidative stress	↑: T-SOD (serum), *Turicibacter*, Ruminococcaceae_UCG_009 (cecum) ↓: Diarrhea rate, TNF-α, IL-6 (jejunum)	Zhang et al. (2020c)
Lactobacillus delbrueckii	Weaned piglets	2.01×10^{10} CFU/g	Oxidative stress	↑: GSH, SOD (jejunal mucosa), GR, GPx (serum & intestinal mucosa), TLRs-Btk-Nrf2 signaling pathway (intestine) ↓: MDA (serum & intestinal mucosa), 8-OHdG (jejunal mucosa)	Chen et al. (2021a)
Pediococcus pentosaceus	Weaning piglets	1×10^8 CFU/mL	Oxidative stress	↑: GPx, SOD, CAT (liver), *Lactobacillus*, Nrf2-Keap1 signaling pathway (liver) ↓: MDA (liver), TP, ALB, LDH, ALT (serum)	Wang et al. (2022)
Lactobacillus reuteri; *Lactobacillus salivarius*	Weaning piglets	3.0×10^6 CFU/g; 1.5×10^6 CFU/g	Weaning stress	↑: *Lactobacillus*, *Acinetobacter*, Ruminococcaceae UCG-014, *Bacteroides*, *Helicobacter*, SOD, CAT, GPx, IFN-α, IFN-β (plasma) ↓: Diarrhea rate, *Escherichia-Shigella*, *Streptococcus*, *Peptoclostridium*, *Clostridium* sensu stricto 1, *Fusobacterium*, *Roseburia*, *Veillonella* (ileum & cecum), MDA (plasma)	Yang et al. (2020)

8-OHdG = 8-hydroxy-2-deoxyguanosine; ALB = albumin; ALT = alanine aminotransferase; BPI = bactericidal/permeability-increasing protein; Btk = Bruton's tyrosine kinase; CAT = catalase; C6 = complement component 6; DMBT1 = deleted in malignant brain tumor 1; GSH = glutathione; GPx = glutathione peroxidase; GR = glutathione reductase; Ig = immunoglobulin; IL = interleukin; Keap1 = Kelch-like epichlorohydrin-associated protein 1; LDH = lactic dehydrogenase; LUM = lumican; MDA = malondialdehyde; Nrf2 = nuclear factor erythroid 2-related factor 2; OLFM4 = Olfactomedin 4; RSAD2 = radical SAM domain-containing 2; SLPI = secretory leukocyte protease inhibitor; SOD = superoxide dismutase; TLRs = toll-like receptors; TNF = tumor necrosis factor; TP = total protein.

Table 7
Summary of studies about the application of minerals and vitamins in stress-resistance of swine.

Minerals/ Vitamins	Pig	Dose	Stress type	Effect	Reference
Cr	Finishing pigs	200 μg/kg	Heat stress	↑: Neutrophils	Mayorga et al. (2019)
Fe	Neonatal piglets	60 mg/kg	Oxidative stress	↑: Hepcidin mRNA, IL-6, IFN-γ, IL-1β, TGF-β, pBD-1 (ileum)	Pu et al. (2018)
Se	Boars	1 mg/kg	Oxidative stress	↑: selenoprotein S mRNA, GPx (liver) ↓: ALT, AST (serum), the content of MDA (liver), the ratio of apoptotic cells (liver)	Wang et al. (2020a)
Se	Gilts	1 mg/kg	Heat stress	↑: GPx (erythrocyte) ↓: Rectal temperature	Liu et al. (2018a)
Se	Sows and piglets	0.04 mg/kg; 0.06 mg/kg	Oxidative stress	↑: γ-glutamyl transferase, GPx3 (plasma) ↓: Red blood cell counts, hemoglobin, hematocrit	Falk et al. (2020)
Se	Sows	1 mg/kg	Oxidative stress	↑: GSH, SOD (colostrum), GPx (colostrum and 14-d milk) ↓: MDA (colostrum and 14-d milk)	Zhang et al. (2020b)
Vitamin A	Weaned piglets	13,500 IU/kg	Weaning stress	↑: Retinol, IgM, IgA, GPx (serum)	Hu et al. (2020)
Vitamin A	Nursing piglets	No data	Immune stress	↑: IL-10, IFN-α, IFN-γ (serum), IgA IgSCs (serum), $IgA^+ \beta7^+$ B cells (milk)	Langel et al. (2019)
Vitamin C	Weaning piglets	150 mg/kg	Oxidative stress	↑: PXR mRNA, CAR mRNA, GPx, T-AOC, SOD (liver) ↓: MDA (liver)	Shi et al. (2017)
Vitamin E	Growing pigs	50, 100, 200 IU/kg	Heat stress	↑: GPx-2 mRNA, GPx (jejunum & ileum) ↓: GSSG: GSH	Liu et al. (2016)
Vitamin E	Multiparous sows	200 IU/kg	Oxidative stress	↑: GPx (serum), SOD (serum) ↓: MDA (serum)	Wang et al. (2019c)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAR = constitutive androstane receptor; GPx = glutathione peroxidase; GSH = glutathione; GSSG = glutathione disulfide; Ig = immunoglobulin; IL = interleukin; IgSCs = immunoglobulin secreting cells; MDA = malondialdehyde; pBD = porcine beta-defensin; PXR = pregnane x receptors; SOD = superoxide dismutase; T-AOC = total antioxidant capacity; TGF = transforming growth factor.

supplemented Se at 1 mg/kg for these pigs at the age of 40 days, reducing the activity of alanine aminotransferase and aspartate aminotransferase in serum, as well as the content of MDA and the ratio of apoptotic cells in the liver. Noteworthily, the absorption efficiency and feasibility are influenced by substance sources. Compared to inorganic minerals, organic minerals have higher bioavailability and lower fecal mineral excretion in animals. Zinc glycine chelate is a good source for zinc fortification to improve growth performance in weaning piglets (Wang et al., 2010). Growing-finishing pigs fed methionine hydroxyl analog chelated microminerals (Cu, Fe, Mn, Zn) had higher immune function and antioxidant status, compared with a group fed inorganic microminerals (Chen et al., 2022b). The antioxidant mechanism of vitamins in swine has been summarized in a review (Hao et al., 2021). Vitamin E and selenoproteins are both known dietary antioxidants which influence immunological functions by converting ROS into non-reactive forms (Hidiroglou et al., 1992; Falk et al., 2020). Supplementation of 200 IU/kg vitamin E and 1.0 mg/kg Se together increased the activity of GPx and the GSH:GSSG ratio, which relieved intestinal barrier damage in heat-stressed growing pigs (Liu et al., 2016). To alleviate liver damage caused by zearalenone, dietary supplementation with 150 mg/kg vitamin C reduced the MDA level and increased the level of SOD in livers of weaning piglets (Shi et al., 2017). Oral supplementation of vitamin A (30,000 IU retinyl acetate) in gilts infected with porcine epidemic diarrhea virus enhanced the IgA level and lactogenic immune protection of nursing piglets (Langel et al., 2019). The supplementation of 25-hydroxyvitamin D_3 is a feasible option for indoor swine production, which increased vitamin D content and the antioxidant status of pork (Duffy et al., 2018).

Breeders often seek the optimal concentration to achieve lower cost and better growth performance. In the practical application of anti-stress nutritional strategies, dose variation contributes different effects. Given that minerals and vitamins constitute a relatively small percentage of the diet, it is necessary to pay attention to the supplemental dosages to maintain a good foundation of balanced pig nutrition (Yang et al., 2021b). For example, iron overdose can induce diarrhea in piglets (Chen et al., 2020b). When supplemented with 500 mg Fe/kg dry matter, the gut was impaired by increased neutrophil infiltration and intestinal permeability and reduced villus height in the duodenum of weaning piglets (Li et al., 2016b).

3. Conclusion

In summary, improving stress-resistance by supplementing relevant nutrients or optimizing feed formulation is a good practice to enhance the amount of antioxidant enzymes in key signaling pathways and to mitigate damage caused by stress responses in animal production. This review summarized stress inducing factors, experimental models, signaling transduction pathways, and several nutritional strategies in pigs. In practical production, multiple additive blends have been widely reported with complicated modes of action and unexpected advantages (Markowiak et al., 2017). Combined supplementation of 2,000 mg/kg benzoic acid and 100 mg/kg thymol in the diet significantly alleviated post-weaning diarrhea and increased the abundance of *Lactobacillus* spp. in ileal digesta (Diao et al., 2015). Supplementation of 4 mg/kg vitamin B_6 in an 18% low protein diet decreased inflammatory cytokines and increased amino acid transporter expression in the jejunum (Yin et al., 2020). Based on the potential synergistic effect between probiotics and prebiotics, combining *L. plantarum* ZLP001 with FOS decreased the abundance of Enterobacteriaceae spp., while increasing the concentrations of IFN-γ and IgG in serum of weaned piglets (Wang et al., 2019b).

The comprehensive process of stress still needs to be further studied for pig growth performance, animal welfare and related human diseases. Stress is closely related to several human metabolic diseases, including obesity (Jakubiak et al., 2021), diabetes mellitus (Darenskaya et al., 2021), cardiovascular disease (Incalza et al., 2018) and cancer (Sosa et al., 2013). Considering the similarities between pigs and humans in anatomy, physiology and immunology (Lunney et al., 2021), further in-depth elucidation on stress mechanisms and intervention strategies are of great significance to reduce losses due to stress. For long-term sustainability, screening new biomolecules or designing targeted formulas against stress is the precondition and basis to develop cost-effective alternatives in a profitable swine industry. Van den Brink et al. (2015) created an electrochemical microfluidic chip coupled with mass spectrometric detection in antidotal drug discovery. A high through-put sandwiched microarray platform was also developed to screen natural compounds and combinatorial chemistries at cellular level (Parihar et al., 2022). Nowadays, self-organized organoids are recognized as promising preclinical models to pinpoint potential therapeutic agents in many fields without the variations in animal physiology. Using a three-dimensional bioprinting-based organoid culture technique, neurospheres are available to study the role of oxidative stress in neurodegenerative disease progression (Sumien et al., 2021; Parihar et al., 2022). For several epithelial cancers, MCLA-158 was selected as a therapeutic EGFR $\times$ LGR5 bispecific antibody from patient-derived organoids (Goto et al., 2022). Organoids derived from animal intestinal epithelial cells have been used for screening potential additives (Yin et al., 2019). Curcumin was selected from common dietary nutrients to promote the intestinal development in murine intestinal organoids (Cai et al., 2018). As considerable progress has been made, researchers in traditional animal nutrition are expected to embrace the challenges and opportunities to select more effective anti-stress preparations through complex devices and novel models.

Author contributions

Leli Wang: Conceptualization, Writing—editing. **Chuni Wang:** Writing—original draft preparation—editing. **Yao Peng:** Writing—original draft preparation. **Yiru Zhang:** Editing. **Yuxin Liu:** Editing. **Yan Liu:** Editing. **Yulong Yin:** Conceptualization, Writing—reviewing & editing, Funding acquisition, Supervision.

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. There is no professional or other personal interest of any nature or kind in any product, service or company that could be construed as influencing the content of this paper.

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References

Armendariz-Barragan B, Zafar N, Badri W, Galindo-Rodriguez SA, Kabbaj D, Fessi H, Elaissari A. Plant extracts: from encapsulation to application. Expet Opin Drug Deliv 2016;13(8):1165–75. https://doi.org/10.1080/17425247.2016.1182487.
Bajaj BK, Claes IJJ, Lebeer S. In: Functional mechanisms of probiotics. Faculty of Biotechnology and Food SciencesSlovak, 4. University of Agriculture; 2015. p. 321–7. https://doi.org/10.15414/jmbfs.2015.4.4.321-327.
Baker DH. Advances in protein-amino acid nutrition of poultry. Amino Acids 2009;37(1):29–41. https://doi.org/10.1007/s00726-008-0198-3.
Bakker GC, Dekker RA, Jongbloed R, Jongbloed AW. Non-starch polysaccharides in pig feeding. Vet Q 1998;20(Suppl 3):S59–64.
Baltić B, Starčević M, Đorđević J, Mrdović B, Marković R. Importance of medium chain fatty acids in animal nutrition. IOP Conf Ser Earth Environ Sci 2017;85(1): 012048. https://doi.org/10.1088/1755-1315/85/1/012048.
Bao M, Liang M, Sun X, Mohyuddin SG, Chen S, Wen J, Yong Y, Ma X, Yu Z, Ju X, Liu X. Baicalin alleviates LPS-induced oxidative stress via NF-kappaB and Nrf2-HO1 signaling pathways in IPEC-J2 cells. Front Vet Sci 2021;8:808233. https://doi.org/10.3389/fvets.2021.808233.
Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. gamma-Aminobutyric acid production by culturable bacteria from the human intestine. J Appl Microbiol 2012;113(2):411–7. https://doi.org/10.1111/j.1365-2672.2012.05344.x.

Baumgard LH, Rhoads Jr RP. Effects of heat stress on postabsorptive metabolism and energetics. Annu Rev Anim Biosci 2013;1:311–37. https://doi.org/10.1146/annurev-animal-031412-103644.
Bayliak MM, Lushchak VI. Pleiotropic effects of alpha-ketoglutarate as a potential anti-ageing agent. Ageing Res Rev 2021;66:101237. https://doi.org/10.1016/j.arr.2020.101237.
Bell AW, Ehrhardt RA. Regulation of placental nutrient transport and implications for fetal growth. Nutr Res Rev 2002;15(2):211–30. https://doi.org/10.1079/nrr200239.
Bi C, Yin J, Yang W, Shi B, Shan A. Effects of dietary gamma-aminobutyric acid supplementation on antioxidant status, blood hormones and meat quality in growing-finishing pigs undergoing transport stress. J Anim Physiol Anim Nutr 2020;104(2):590–6. https://doi.org/10.1111/jpn.13280.
Biggs ME, Kroscher KA, Zhao LD, Zhang Z, Wall EH, Bravo DM, et al. Dietary supplementation of artificial sweetener and capsicum oleoresin as a strategy to mitigate the negative consequences of heat stress on pig performance. J Anim Sci 2020;98(5). https://doi.org/10.1093/jas/skaa131.
Bland EJ, Keshavarz T, Bucke C. The influence of small oligosaccharides on the immune system. Carbohydr Res 2004;339(10):1673–8. https://doi.org/10.1016/j.carres.2004.05.009.
Bonetti A, Tugnoli B, Rossi B, Giovagnoni G, Piva A, Grilli E. Nature-identical compounds and organic acids reduce E. coli K88 growth and virulence gene expression in vitro. Toxins 2020;12(8). https://doi.org/10.3390/toxins12080468.
Briskey EJ. Etiological status and associated studies of pale, soft, exudative porcine musculature. Adv Food Res 1964;13:89–178. https://doi.org/10.1016/s0065-2628(08)60100-7.
Brunton JA, Bertolo RF, Pencharz PB, Ball RO. Proline ameliorates arginine deficiency during enteral but not parenteral feeding in neonatal piglets. Am J Physiol 1999;277(2):E223–31. https://doi.org/10.1152/ajpendo.1999.277.2.E223.
Burrin DG, Stoll B. Metabolic fate and function of dietary glutamate in the gut. Am J Clin Nutr 2009;90(3):850s–6s. https://doi.org/10.3945/ajcn.2009.27462Y.
Cai L, Wei Z, Zhao X, Li Y, Li X, Jiang X. Gallic acid mitigates LPS-induced inflammatory response via suppressing NF-kappaB signalling pathway in IPEC-J2 cells. J Anim Physiol Anim Nutr 2022;106(5):1000–8. https://doi.org/10.1111/jpn.13612.
Cai T, Qi Y, Jergens A, Wannemuehler M, Barrett TA, Wang Q. Effects of six common dietary nutrients on murine intestinal organoid growth. PLoS One 2018;13(2):e0191517. https://doi.org/10.1371/journal.pone.0191517.
Campbell JM, Crenshaw JD, Polo J. The biological stress of early weaned piglets. J Anim Sci Biotechnol 2013;4(1):19. https://doi.org/10.1186/2049-1891-4-19.
Canibe N, Højberg O, Badsberg JH, Jensen BB. Effect of feeding fermented liquid feed and fermented grain on gastrointestinal ecology and growth performance in piglets. J Anim Sci 2007;85(11):2959–71. https://doi.org/10.2527/jas.2006-744.
Canibe N, Jensen BB. Fermented and nonfermented liquid feed to growing pigs: effect on aspects of gastrointestinal ecology and growth performance. J Anim Sci 2003;81(8):2019–31. https://doi.org/10.2527/2003.8182019x.
Cao S, Hou L, Sun L, Gao J, Gao K, Yang X, Jiang Z, Wang L. Intestinal morphology and immune profiles are altered in piglets by early-weaning. Int Immunopharm 2022;105:108520. https://doi.org/10.1016/j.intimp.2022.108520.
Cao S, Shen Z, Wang C, Zhang Q, Hong Q, He Y, Hu C. Resveratrol improves intestinal barrier function, alleviates mitochondrial dysfunction and induces mitophagy in diquat challenged piglets(1). Food Funct 2019;10(1):344–54. https://doi.org/10.1039/c8fo02091d.
Cao S, Wu H, Wang C, Zhang Q, Jiao L, Lin F, Hu CH. Diquat-induced oxidative stress increases intestinal permeability, impairs mitochondrial function, and triggers mitophagy in piglets. J Anim Sci 2018;96(5):1795–805. https://doi.org/10.1093/jas/sky104.
Chae SY, Jang MK, Nah JW. Influence of molecular weight on oral absorption of water soluble chitosans. J Contr Release 2005;102(2):383–94. https://doi.org/10.1016/j.jconrel.2004.10.012.
Chakraborty B, Nath A, Saikia H, Sengupta M. Bactericidal activity of selected medicinal plants against multidrug resistant bacterial strains from clinical isolates. Asian Pac J Tropical Med 2014;7(7S1):S435–41.
Che TM, Johnson RW, Kelley KW, Van Alstine WG, Dawson KA, Moran CA, Pettigrew JE. Mannan oligosaccharide improves immune responses and growth efficiency of nursery pigs experimentally infected with porcine reproductive and respiratory syndrome virus. J Anim Sci 2011;89(8):2592–602. https://doi.org/10.2527/jas.2010-3208.
Chei S, Song JH, Oh HJ, Lee K, Lee BY. Gintonin-enriched fraction suppresses heat stress-induced inflammation through LPA receptor. Molecules 2020;25(5):1019.
Chen F, Chen J, Chen Q, Yang L, Yin J, Li Y, Huang X. Lactobacillus delbrueckii protected intestinal integrity, alleviated intestinal oxidative damage, and activated toll-like receptor-bruton's tyrosine kinase-nuclear factor erythroid 2-related factor 2 pathway in weaned piglets challenged with lipopolysaccharide. Antioxidants (Basel) 2021a;10(3). https://doi.org/10.3390/antiox10030468.
Chen G, Shui S, Chai M, Wang D, Su Y, Wu H, Sui X, Yin Y. Effects of paper mulberry (broussonetia papyrifera) leaf extract on growth performance and fecal microflora of weaned piglets. BioMed Res Int 2020a;2020:6508494. https://doi.org/10.1155/2020/6508494.
Chen H, Zhang Y, Zou M, Sun X, Huang X, Xu S. Dibutyl phthalate-induced oxidative stress and apoptosis in swine testis cells and therapy of naringenin via PTEN/PI3K/AKT signaling pathway. Environ Toxicol 2022a;37(8):1840–52. https://doi.org/10.1002/tox.23531.
Chen J, Li Y, Tian Y, Huang C, Li D, Zhong Q, et al. Interaction between microbes and host intestinal health: modulation by dietary nutrients and gut-brain-endocrine-immune Axis. Current protein & peptide science 2015;16(7):592–603. https://doi.org/10.2174/1389203716666150630135720.
Chen J, Li Y, Yu B, Chen D, Mao X, Zheng P, Luo J, He J. Dietary chlorogenic acid improves growth performance of weaned pigs through maintaining antioxidant capacity and intestinal digestion and absorption function. J Anim Sci 2018a;96(3):1108–18. https://doi.org/10.1093/jas/skx078.
Chen J, Wang H, Ma Y, Zhang Y, Wang S, Zang J. Effects of the methionine hydroxyl analog chelated microminerals on growth performance, antioxidant status, and immune response of growing-finishing pigs. Anim Sci J 2022b;93(1):e13730. https://doi.org/10.1111/asj.13730.
Chen J, Xu Q, Li Y, Tang Z, Sun W, Zhang X, Sun J, Sun Z. Comparative effects of dietary supplementations with sodium butyrate, medium-chain fatty acids, and n-3 polyunsaturated fatty acids in late pregnancy and lactation on the reproductive performance of sows and growth performance of suckling piglets. J Anim Sci 2019a;97(10):4256–67. https://doi.org/10.1093/jas/skz284.
Chen JQ, Li YS, Li ZJ, Lu HX, Zhu PQ, Li CM. Dietary l-arginine supplementation improves semen quality and libido of boars under high ambient temperature. Animal 2018b;12(8):1611–20. https://doi.org/10.1017/s1751731117003147.
Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2018c;9(6):7204–18. https://doi.org/10.18632/oncotarget.23208.
Chen S, Tan B, Xia Y, Liao S, Wang M, Yin J, Wang J, Xiao H, Qi M, Bin P, Liu G, Ren W, Yin Y. Effects of dietary gamma-aminobutyric acid supplementation on the intestinal functions in weaning piglets. Food Funct 2019b;10(1):366–78. https://doi.org/10.1039/c8fo02161a.
Chen S, Wu X, Wang X, Shao Y, Tu Q, Yang H, Yin J, Yin Y. Responses of intestinal microbiota and immunity to increasing dietary levels of iron using a piglet model. Front Cell Dev Biol 2020b;8:603392. https://doi.org/10.3389/fcell.2020.603392.
Chen S, Wu X, Xia Y, Wang M, Liao S, Li F, Yin J, Ren W, Tan B, Yin Y. Effects of dietary gamma-aminobutyric acid supplementation on amino acid profile, intestinal immunity, and microbiota in ETEC-challenged piglets. Food Funct 2020c;11(10):9067–74. https://doi.org/10.1039/d0fo01729a.
Chen X, Wang Y, Shen M, Yu Q, Chen Y, Huang L, Xie J. The water-soluble non-starch polysaccharides from natural resources against excessive oxidative stress: a potential health-promoting effect and its mechanisms. Int J Biol Macromol 2021b;171:320–30. https://doi.org/10.1016/j.ijbiomac.2021.01.022.
Cho HY, Reddy SP, Kleeberger SR. Nrf2 defends the lung from oxidative stress. Antioxidants Redox Signal 2006;8(1–2):76–87. https://doi.org/10.1089/ars.2006.8.76.
Cho JH, Zhao PY, Kim IH. Probiotics as a dietary additive for pigs: a review. J Anim Vet Adv 2011;10(16):2127–34. https://doi.org/10.3923/javaa.2011.2127.2134.
Choi J, Wang L, Liu S, Lu P, Zhao X, Liu H, Lahaye L, Santin E, Liu S, Nyachoti M, Yang C. Effects of a microencapsulated formula of organic acids and essential oils on nutrient absorption, immunity, gut barrier function, and abundance of enterotoxigenic Escherichia coli F4 in weaned piglets challenged with E. coli F4. J Anim Sci 2020;98(9). https://doi.org/10.1093/jas/skaa259.
Clark AM. Natural products as a resource for new drugs. Pharm Res 1996;13(8):1133–44. https://doi.org/10.1023/a:1016091631721.
Corino C, Modina SC, Di Giancamillo A, Chiapparini S, Rossi R. Seaweeds in pig nutrition. Animals (Basel) 2019;9(12). https://doi.org/10.3390/ani9121126.
Costilla M, Macri Delbono R, Klecha A, Cremaschi GA, Barreiro Arcos ML. Oxidative stress produced by hyperthyroidism status induces the antioxidant enzyme transcription through the activation of the Nrf-2 factor in lymphoid tissues of balb/c mice. Oxid Med Cell Longev 2019;2019:7471890. https://doi.org/10.1155/2019/7471890.
Csernus B, Czegledi L. Physiological, antimicrobial, intestine morphological, and immunological effects of fructooligosaccharides in pigs. Arch Anim Breed 2020;63(2):325–35. https://doi.org/10.5194/aab-63-325-2020.
Czech A, Grela ER, Mokrzycka A, Pejsak Z. Efficacy of mannanoligosaccharides additive to sows diets on colostrum, blood immunoglobulin content and production parameters of piglets. Pol J Vet Sci 2010;13(3):525–31.
Darenskaya MA, Kolesnikova LI, Kolesnikov SI. Oxidative stress: pathogenetic role in diabetes mellitus and its complications and therapeutic approaches to correction. Bull Exp Biol Med 2021;171(2):179–89. https://doi.org/10.1007/s10517-021-05191-7.
de Jesus Raposo MF, de Morais AM, de Morais RM. Emergent sources of prebiotics: seaweeds and microalgae. Mar Drugs 2016;14(2). https://doi.org/10.3390/md14020027.
Decuypere JA, Dierick NA. The combined use of triacylglycerols containing medium-chain fatty acids and exogenous lipolytic enzymes as an alternative to in-feed antibiotics in piglets: concept, possibilities and limitations. An overview. Nutr Res Rev 2003;16(2):193–210. https://doi.org/10.1079/nrr200369.
Del Olmo A, Calzada J, Nuñez M. Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: uses, exposure, and controversy. Crit Rev Food Sci Nutr 2017;57(14):3084–103. https://doi.org/10.1080/10408398.2015.1087964.
Diamond-Stanic MK, Marchionne EM, Teachey MK, Durazo DE, Kim JS, Henriksen EJ. Critical role of the transient activation of p38 MAPK in the etiology of skeletal muscle insulin resistance induced by low-level in vitro oxidant stress. Biochem Biophys Res Commun 2011;405(3):439–44. https://doi.org/10.1016/j.bbrc.2011.01.049.
Diao H, Gao Z, Yu B, Zheng P, He J, Yu J, Huang Z, Chen D, Mao X. Effects of benzoic acid (VevoVitall®) on the performance and jejunal digestive physiology in

young pigs. J Anim Sci Biotechnol 2016;7:32. https://doi.org/10.1186/s40104-016-0091-y.
Diao H, Jiao AR, Yu B, Mao XB, Chen DW. Gastric infusion of short-chain fatty acids can improve intestinal barrier function in weaned piglets. Genes Nutr 2019;14:4. https://doi.org/10.1186/s12263-019-0626-x.
Diao H, Zheng P, Yu B, He J, Mao X, Yu J, Chen D. Effects of benzoic Acid and thymol on growth performance and gut characteristics of weaned piglets. Asian-Australas J Anim Sci 2015;28(6):827–39. https://doi.org/10.5713/ajas.14.0704.
Diao Y, Xin Y, Zhou Y, Li N, Pan X, Qi S, Qi Z, Xu Y, Luo L, Wan H, Lan L, Yin Z. Extracellular polysaccharide from Bacillus sp. strain LBP32 prevents LPS-induced inflammation in RAW 264.7 macrophages by inhibiting NF-kappaB and MAPKs activation and ROS production. Int Immunopharm 2014;18(1):12–9. https://doi.org/10.1016/j.intimp.2013.10.021.
Dias JM, de Brito TV, de Aguiar Magalhaes D, da Silva Santos PW, Batista JA, do Nascimento Dias EG, de Barros Fernandes H, Damasceno SR, Silva RO, Aragao KS, Souza MH, Medeiros JV, Barbosa AL. Gabapentin, a synthetic analogue of gamma aminobutyric acid, reverses systemic acute inflammation and oxidative stress in mice. Inflammation 2014;37(5):1826–36. https://doi.org/10.1007/s10753-014-9913-2.
Duan J, Yin J, Ren W, Liu T, Cui Z, Huang X, Wu L, Kim SW, Liu G, Wu X, Wu G, Li T, Yin Y. Dietary supplementation with L-glutamate and L-aspartate alleviates oxidative stress in weaned piglets challenged with hydrogen peroxide. Amino Acids 2016;48(1):53–64. https://doi.org/10.1007/s00726-015-2065-3.
Duan X, Tian G, Chen D, Huang L, Zhang D, Zheng P, Mao X, Yu J, He J, Huang Z, Yu B. Mannan oligosaccharide supplementation in diets of sow and (or) their offspring improved immunity and regulated intestinal bacteria in piglet1. J Anim Sci 2019a;97(11):4548–56. https://doi.org/10.1093/jas/skz318.
Duan Y, Zhao Y, Zhu Q, Cai Q, Li H, Yin Y, Wang Z, Kong X. Dietary nutrient levels alter the metabolism of arginine family amino acids in the conceptus of Huanjiang mini-pigs. J Sci Food Agric 2019b;99(5):2132–9. https://doi.org/10.1002/jsfa.9405.
Duffy SK, Kelly AK, Rajauria G, Jakobsen J, Clarke LC, Monahan FJ, Dowling KG, Hull G, Galvin K, Cashman KD, Hayes A, O'Doherty JV. The use of synthetic and natural vitamin D sources in pig diets to improve meat quality and vitamin D content. Meat Sci 2018;143:60–8. https://doi.org/10.1016/j.meatsci.2018.04.014.
Fairbrother JM, Nadeau E, Gyles CL. Escherichia coli in postweaning diarrhea in pigs: an update on bacterial types, pathogenesis, and prevention strategies. Anim Health Res Rev 2005;6(1):17–39. https://doi.org/10.1079/ahr2005105.
Falk M, Bernhoft A, Reinoso-Maset E, Salbu B, Lebed P, Framstad T, Fuhrmann H, Oropeza-Moe M. Beneficial antioxidant status of piglets from sows fed selenomethionine compared with piglets from sows fed sodium selenite. J Trace Elem Med Biol 2020;58:126439. https://doi.org/10.1016/j.jtemb.2019.126439.
Fan P, Liu P, Song P, Chen X, Ma X. Moderate dietary protein restriction alters the composition of gut microbiota and improves ileal barrier function in adult pig model. Sci Rep 2017;7:43412. https://doi.org/10.1038/srep43412.
Farmer C, Lapointe J, Palin MF. Effects of the plant extract silymarin on prolactin concentrations, mammary gland development, and oxidative stress in gestating gilts. J Anim Sci 2016;92(7):2922–30. https://doi.org/10.2527/jas.2013-7118.
Favas R, Morone J, Martins R, Vasconcelos V, Lopes G. Cyanobacteria secondary metabolites as biotechnological ingredients in natural anti-aging cosmetics: potential to overcome hyperpigmentation, loss of skin density and UV radiation-deleterious effects. Mar Drugs 2022;20(3). https://doi.org/10.3390/md20030183.
Ferronato G, Prandini A. Dietary supplementation of inorganic, organic, and fatty acids in pig: a review. Animals (Basel) 2020;10(10). https://doi.org/10.3390/ani10101740.
Flynn NE, Knabe DA, Mallick BK, Wu G. Postnatal changes of plasma amino acids in suckling pigs. J Anim Sci 2000;78(9):2369–75. https://doi.org/10.2527/2000.7892369x.
Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspect Med 2009;30(1–2):1–12. https://doi.org/10.1016/j.mam.2008.08.006.
Fouhse JM, Yang K, More-Bayona J, Gao Y, Goruk S, Plastow G, Field CJ, Barreda DR, Willing BP. Neonatal exposure to amoxicillin alters long-term immune response despite transient effects on gut-microbiota in piglets. Front Immunol 2019;10:2059. https://doi.org/10.3389/fimmu.2019.02059.
Gaggia F, Mattarelli P, Biavati B. Probiotics and prebiotics in animal feeding for safe food production. Int J Food Microbiol 2010;141(Suppl 1):S15–28. https://doi.org/10.1016/j.ijfoodmicro.2010.02.031.
Gao F, Jiang Y, Zhou G, Zheng H, Xu Z. Effect of fructooligosaccharides(FOS)on growth,metabolism and immune in weaning piglets. Anim Husb Vet Med 2001;33:8–9.
Gao J, Liu Z, Wang C, Ma L, Chen Y, Li T. Effects of dietary protein level on the microbial composition and metabolomic profile in postweaning piglets. Oxid Med Cell Longev 2022;2022:3355687. https://doi.org/10.1155/2022/3355687.
Gardner AS, Rahman IA, Lai CT, Hepworth A, Trengove N, Hartmann PE, Geddes DT. Changes in fatty acid composition of human milk in response to cold-like symptoms in the lactating mother and infant. Nutrients 2017;9(9). https://doi.org/10.3390/nu9091034.
Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995;125(6):1401–12. https://doi.org/10.1093/jn/125.6.1401.
Giesting DW, Easter RA. Response of starter pigs to supplementation of corn-soybean meal diets with organic acids. J Anim Sci 1985;60(5):1288–94. https://doi.org/10.2527/jas1985.6051288x.
Gloaguen M, Le Floc'h N, Corrent E, Primot Y, van Milgen J. The use of free amino acids allows formulating very low crude protein diets for piglets. J Anim Sci 2014;92(2):637–44. https://doi.org/10.2527/jas.2013-6514.
Gonzalez-Rivas PA, Chauhan SS, Ha M, Fegan N, Dunshea FR, Warner RD. Effects of heat stress on animal physiology, metabolism, and meat quality: a review. Meat Sci 2020;162:108025. https://doi.org/10.1016/j.meatsci.2019.108025.
Goto N, Yilmaz OH. Bispecific antibodies seek out colon cancer stem cells. Nat Can (Ott) 2022;3(4):379–80. https://doi.org/10.1038/s43018-022-00368-z.
Grummer RH, Bentley OG, Phillips PH, Bohstedt. The role of manganese in growth, reproduction, and lactation of swine. J Anim Sci 1950;9(2):170–5. https://doi.org/10.2527/jas1950.92170x.
Guo J, Liang T, Chen H, Li X, Ren X, Wang X, Xiao K, Zhao J, Zhu H, Liu Y. Glutamate attenuates lipopolysaccharide induced intestinal barrier injury by regulating corticotropin-releasing factor pathway in weaned pigs. Anim Biosci 2022;35(8):1235–49. https://doi.org/10.5713/ab.21.0476.
Gyanwali B, Lim ZX, Soh J, Lim C, Guan SP, Goh J, Maier AB, Kennedy BK. Alpha-Ketoglutarate dietary supplementation to improve health in humans. Trends Endocrinol Metabol 2022;33(2):136–46. https://doi.org/10.1016/j.tem.2021.11.003.
Hales JR, Rowell LB, King RB. Regional distribution of blood flow in awake heat-stressed baboons. Am J Physiol 1979;237(6):H705–12. https://doi.org/10.1152/ajpheart.1979.237.6.H705.
Han M, Song P, Huang C, Rezaei A, Farrar S, Brown MA, Ma X. Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model. Oncotarget 2016;7(49):80313–26. https://doi.org/10.18632/oncotarget.13450.
Hao Y, Xing M, Gu X. Research progress on oxidative stress and its nutritional regulation strategies in pigs. Animals (Basel) 2021;11(5). https://doi.org/10.3390/ani11051384.
Hayakawa S, Ohishi T, Miyoshi N, Oishi Y, Nakamura Y, Isemura M. Anti-cancer effects of green tea epigallocatchin-3-gallate and coffee chlorogenic acid. Molecules 2020;25(19). https://doi.org/10.3390/molecules25194553.
Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. Cell 2008;132(3):344–62. https://doi.org/10.1016/j.cell.2008.01.020.
He J, Zhang P, Shen L, Niu L, Tan Y, Chen L, Zhao Y, Bai L, Hao X, Li X, Zhang S, Zhu L. Short-chain fatty acids and their association with signalling pathways in inflammation, glucose and lipid metabolism. Int J Mol Sci 2020;21(17). https://doi.org/10.3390/ijms21176356.
Health EPoA, Welfare, Nielsen SS, Alvarez J, Bicout DJ, Calistri P, Canali E, Drewe JA, Garin-Bastuji B, Gonzales Rojas JL, Schmidt CG, Michel V, Miranda Chueca MA, Padalino B, Pasquali P, Roberts HC, Spoolder H, Stahl K, Velarde A, Viltrop A, Winckler C, Earley B, Edwards S, Faucitano L, Marti S, de La Lama GCM, Costa LN, Thomsen PT, Ashe S, Mur L, Van der Stede Y, Herskin M. Welfare of pigs during transport. EFSA J 2022;20(9):e07445. https://doi.org/10.2903/j.efsa.2022.7445.
Heo JM, Kim JC, Hansen CF, Mullan BP, Hampson DJ, Pluske JR. Effects of feeding low protein diets to piglets on plasma urea nitrogen, faecal ammonia nitrogen, the incidence of diarrhoea and performance after weaning. Arch Anim Nutr 2008;62(5):343–58. https://doi.org/10.1080/17450390802327811.
Hidiroglou N, Cave N, Atwall AS, Farnworth ER, McDowell LR. Comparative vitamin E requirements and metabolism in livestock. Ann Rech Vet 1992;23(4):337–59.
Ho YS, Xiong Y, Ma W, Spector A, Ho DS. Mice lacking catalase develop normally but show differential sensitivity to oxidant tissue injury. J Biol Chem 2004;279(31):32804–12.
Hong J, Fang LH, Jeong JH, Kim YY. Effects of L-arginine supplementation during late gestation on reproductive performance, piglet uniformity, blood profiles, and milk composition in high prolific sows. Animals (Basel) 2020;10(8). https://doi.org/10.3390/ani10081313.
Hou Y, Wang L, Ding B, Liu Y, Zhu H, Liu J, Li Y, Kang P, Yin Y, Wu G. Alpha-Ketoglutarate and intestinal function. Front Biosci (Landmark Ed) 2011a;16(3):1186–96. https://doi.org/10.2741/3783.
Hou Y, Wang L, Ding B, Liu Y, Zhu H, Liu J, Li Y, Wu X, Yin Y, Wu G. Dietary alpha-ketoglutarate supplementation ameliorates intestinal injury in lipopolysaccharide-challenged piglets. Amino Acids 2010;39(2):555–64. https://doi.org/10.1007/s00726-010-0473-y.
Hou Y, Wu G. L-Glutamate nutrition and metabolism in swine. Amino Acids 2018;50(11):1497–510. https://doi.org/10.1007/s00726-018-2634-3.
Hou Y, Yao K, Wang L, Ding B, Fu D, Liu Y, Zhu H, Liu J, Li Y, Kang P, Yin Y, Wu G. Effects of α-ketoglutarate on energy status in the intestinal mucosa of weaned piglets chronically challenged with lipopolysaccharide. Br J Nutr 2011b;106(3):357–63. https://doi.org/10.1017/s0007114511000249.
Hu P, Yang H, Lv B, Zhao D, Wang J, Zhu W. Dynamic changes of fatty acids and minerals in sow milk during lactation. J Anim Physiol Anim Nutr 2019;103(2):603–11. https://doi.org/10.1111/jpn.13040.
Hu T, Lei Y, Li M, Liu Q, Song L, Zhao D. Dietary Eucommia ulmoides extract alleviates the effect of cold stress on chick growth performance, antioxidant and immune ability. Animals (Basel) 2021;11(11). https://doi.org/10.3390/ani11113008.
Hu Y, Zhang L, Zhang Y, Xiong H, Wang F, Wang Y, Lu Z. Effects of starch and gelatin encapsulated vitamin A on growth performance, immune status and antioxidant capacity in weaned piglets. Anim Nutr 2020;6(2):130–3. https://doi.org/10.1016/j.aninu.2020.01.005.
Huang C, Song P, Fan P, Hou C, Thacker P, Ma X. Dietary sodium butyrate decreases postweaning diarrhea by modulating intestinal permeability and changing the bacterial communities in weaned piglets. J Nutr 2015;145(12):2774–80. https://doi.org/10.3945/jn.115.217406.

Hui KK, Tanaka M. Autophagy links MTOR and GABA signaling in the brain. Autophagy 2019;15(10):1848−9. https://doi.org/10.1080/15548627.2019.1637643.
Hyeon S, Lee H, Yang Y, Jeong W. Nrf2 deficiency induces oxidative stress and promotes RANKL-induced osteoclast differentiation. Free Radic Biol Med 2013;65:789−99. https://doi.org/10.1016/j.freeradbiomed.2013.08.005.
Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vasc Pharmacol 2018;100:1−19. https://doi.org/10.1016/j.vph.2017.05.005.
Isaacson R, Kim HB. The intestinal microbiome of the pig. Anim Health Res Rev 2012;13(1):100−9. https://doi.org/10.1017/S1466252312000084.
Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, Oyake T, Hayashi N, Satoh K, Hatayama I, Yamamoto M, Nabeshima Y. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun 1997;236(2):313−22. https://doi.org/10.1006/bbrc.1997.6943.
Jackman JA, Boyd RD, Elrod CC. Medium-chain fatty acids and monoglycerides as feed additives for pig production: towards gut health improvement and feed pathogen mitigation. J Anim Sci Biotechnol 2020;11:44. https://doi.org/10.1186/s40104-020-00446-1.
Jacobsen C, Sorensen AM, Holdt SL, Akoh CC, Hermund DB. Source, extraction, characterization, and applications of novel antioxidants from seaweed. Annu Rev Food Sci Technol 2019;10:541−68. https://doi.org/10.1146/annurev-food-032818-121401.
Jain L. Stress at birth and its inextricable link to the neonatal transition. Obstet Gynecol 2016;128(4):685−7. https://doi.org/10.1097/AOG.0000000000001657.
Jakubiak GK, Osadnik K, Lejawa M, Kasperczyk S, Osadnik T, Pawlas N. Oxidative stress in association with metabolic health and obesity in young adults. Oxid Med Cell Longev 2021;2021:9987352. https://doi.org/10.1155/2021/9987352.
Jean KB, Chiang SH. Increased survival of neonatal pigs by supplementing medium-chain triglycerides in late-gestating sow diets. Anim Feed Sci Technol 1999;76(3−4):241−50.
Jia AF, Feng JH, Zhang MH, Chang Y, Li ZY, Hu CH, Zhen L, Zhang SS, Peng QQ. Effects of immunological challenge induced by lipopolysaccharide on skeletal muscle fiber type conversion of piglets. J Anim Sci 2015;93(11):5194−203. https://doi.org/10.2527/jas.2015-9391.
Jiang L, Wang W, Wen P, Shen M, Xie J. Two water-soluble polysaccharides from mung bean skin: physicochemical characterization, antioxidant and antibacterial activities. Food Hydrocolloids 2019;100:105412.
Jin J, Zhang L, Jia J, Chen Q, Yuan Z, Zhang X, Sun W, Ma C, Xu F, Zhan S, Ma L, Zhou G. Effects of maternal low-protein diet on microbiota structure and function in the jejunum of huzhu bamei suckling piglets. Animals (Basel) 2019;9(10). https://doi.org/10.3390/ani9100713.
Johnson W, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, Andersen FA. Safety assessment of benzyl alcohol, benzoic acid and its salts, and benzyl benzoate. Int J Toxicol 2017;36(3_suppl):5s−30s. https://doi.org/10.1177/1091581817728996.
Joshi DS, Singhvi MS, Khire JM, Gokhale DV. Strain improvement of Lactobacillus lactis for D-lactic acid production. Biotechnol Lett 2010;32(4):517−20. https://doi.org/10.1007/s10529-009-0187-y.
Kaizu H, Sasaki M, Nakajima H, Suzuki Y. Effect of antioxidative lactic acid bacteria on rats fed a diet deficient in vitamin E. J Dairy Sci 1993;76(9):2493−9. https://doi.org/10.3168/jds.S0022-0302(93)77584-0.
Kemp B, Soede NM. Reproductive issues in welfare-friendly housing systems in pig husbandry: a review. Reprod Domest Anim 2012;47(Suppl 5):51−7. https://doi.org/10.1111/j.1439-0531.2012.02108.x.
Kianian F, Seifi B, Kadkhodaee M, Sadeghipour HR, Ranjbaran M. Nephroprotection through modifying the apoptotic TNF-α/ERK1/2/bax signaling pathway and oxidative stress by long-term sodium hydrosulfide administration in ovalbumin-induced chronic asthma. J Mol Cell Immunol 2022:51(3):602−618. https://doi.org/10.1080/08820139.2020.1858860.
Kim J, Kim J, Kim Y, Oh S, Song M, Choe JH, Whang KY, Kim KH, Oh S. Influences of quorum-quenching probiotic bacteria on the gut microbial community and immune function in weaning pigs. Anim Sci J 2018;89(2):412−22. https://doi.org/10.1111/asj.12954.
Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, Guigó R, Gladyshev VN. Characterization of mammalian selenoproteomes. Science 2003;300(5624):1439−43. https://doi.org/10.1126/science.1083516.
Kullisaar T, Songisepp E, Mikelsaar M, Zilmer K, Vihalemm T, Zilmer M. Antioxidative probiotic fermented goats' milk decreases oxidative stress-mediated atherogenicity in human subjects. Br J Nutr 2003;90(2):449−56. https://doi.org/10.1079/bjn2003896.
Kullisaar T, Zilmer M, Mikelsaar M, Vihalemm T, Annuk H, Kairane C, Kilk A. Two antioxidative lactobacilli strains as promising probiotics. Int J Food Microbiol 2002;72(3):215−24. https://doi.org/10.1016/s0168-1605(01)00674-2.
Lambert GP. Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. J Anim Sci 2009;87(14 Suppl):E101−8. https://doi.org/10.2527/jas.2008-1339.
Lan R, Kim I. Effects of feeding diets containing essential oils and betaine to heat-stressed growing-finishing pigs. Arch Anim Nutr 2018;72(5):368−78. https://doi.org/10.1080/1745039X.2018.1492806.
Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. Publ Health Rep 2012;127(1):4−22. https://doi.org/10.1177/003335491212700103.
Landis GN, Tower J. Superoxide dismutase evolution and life span regulation. Mech Ageing Dev 2005;126(3):365−79. https://doi.org/10.1016/j.mad.2004.08.012.
Langel SN, Paim FC, Alhamo MA, Lager KM, Vlasova AN, Saif LJ. Oral vitamin A supplementation of porcine epidemic diarrhea virus infected gilts enhances IgA and lactogenic immune protection of nursing piglets. Vet Res 2019;50(1):101. https://doi.org/10.1186/s13567-019-0719-y.
Langendijk P. Latest advances in sow nutrition during early gestation. Animals (Basel) 2021;11(6). https://doi.org/10.3390/ani11061720.
Lauridsen C. From oxidative stress to inflammation: redox balance and immune system. Poultry Sci 2019;98(10):4240−6. https://doi.org/10.3382/ps/pey407.
Lauridsen C. Effects of dietary fatty acids on gut health and function of pigs pre- and post-weaning. J Anim Sci 2020;98(4). https://doi.org/10.1093/jas/skaa086.
Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harbor Perspect Biol 2009;1(6):a001651. https://doi.org/10.1101/cshperspect.a001651.
Le HH, Shakeri M, Suleria HAR, Zhao W, McQuade RM, Phillips DJ, Vidacs E, Furness JB, Dunshea FR, Artuso-Ponte V, Cottrell JJ. Betaine and isoquinoline alkaloids protect against heat stress and colonic permeability in growing pigs. Antioxidants (Basel) 2020;9(10). https://doi.org/10.3390/antiox9101024.
Lee AV, You L, Oh SY, Li Z, Fisher-Heffernan RE, Regnault TRH, de Lange CFM, Huber L, Karrow NA. Microalgae supplementation to late gestation sows and its effects on the health status of weaned piglets fed diets containing high- or low-quality protein sources. Vet Immunol Immunopathol 2019;218:109937. https://doi.org/10.1016/j.vetimm.2019.109937.
Lee BW, Ha JH, Shin HG, Jeong SH, Kim JH, Lee J, Park JY, Kwon HJ, Jung K, Lee WS, Ryu YB, Jeong JH, Lee IC. Lindera obtusiloba attenuates oxidative stress and airway inflammation in a murine model of ovalbumin-challenged asthma. Antioxidants (Basel) 2020;9(7). https://doi.org/10.3390/antiox9070563.
Lee SI, Kang KS. Function of capric acid in cyclophosphamide-induced intestinal inflammation, oxidative stress, and barrier function in pigs. Sci Rep 2017;7(1):16530. https://doi.org/10.1038/s41598-017-16561-5.
LeMieux FM, Southern LL, Bidner TD. Effect of mannan oligosaccharides on growth performance of weanling pigs. J Anim Sci 2003;81(10):2482−7. https://doi.org/10.2527/2003.81102482x.
Lemuh N.D., Assob J., Ebenye M.S., Jerome N.D., Kwe Y.C., Bertrand S. Antimicrobial activities of a plethora of medicinal plant extracts and hydrolates against human pathogens and their potential to reverse antibiotic resistance. International Journal of Microbiology 2015;2015:15 2015,(2015-5-27). https://doi.org/10.1155/2015/547156
Li C, Wang Y, Li L, Han Z, Mao S, Wang G. Betaine protects against heat exposure-induced oxidative stress and apoptosis in bovine mammary epithelial cells via regulation of ROS production. Cell Stress Chaperones 2019a;24(2):453−60. https://doi.org/10.1007/s12192-019-00982-4.
Li J, Fan Q, Jin M, Mao C, Zhang H, Zhang X, Sun L, Grenier D, Yi L, Hou X, Wang Y. Paeoniflorin reduce luxS/AI-2 system-controlled biofilm formation and virulence in Streptococcus suis. Virulence 2021a;12(1):3062−73. https://doi.org/10.1080/21505594.2021.2010398.
Li N, Huang S, Jiang L, Wang W, Li T, Zuo B, Li Z, Wang J. Differences in the gut microbiota establishment and metabolome characteristics between low- and normal-birth-weight piglets during early-life. Front Microbiol 2018;9:1798. https://doi.org/10.3389/fmicb.2018.01798.
Li R, Hou G, Jiang X, Song Z, Fan Z, Hou DX, He X. Different dietary protein sources in low protein diets regulate colonic microbiota and barrier function in a piglet model. Food Funct 2019b;10(10):6417−28. https://doi.org/10.1039/c9fo01154d.
Li X, Wang C, Zhu J, Lin Q, Yu M, Wen J, Feng J, Hu C. Sodium butyrate ameliorates oxidative stress-induced intestinal epithelium barrier injury and mitochondrial damage through AMPK-mitophagy pathway. Oxid Med Cell Longev 2022;2022:3745135. https://doi.org/10.1155/2022/3745135.
Li XG, Sui WG, Gao CQ, Yan HC, Yin YL, Li HC, Wang XQ. L-Glutamate deficiency can trigger proliferation inhibition via down regulation of the mTOR/S6K1 pathway in pig intestinal epithelial cells. J Anim Sci 2016a;94(4):1541−9. https://doi.org/10.2527/jas.2015-9432.
Li Y, Hansen SL, Borst LB, Spears JW, Moeser AJ. Dietary iron deficiency and over-supplementation increase intestinal permeability, ion transport, and inflammation in pigs. J Nutr 2016b;146(8):1499−505. https://doi.org/10.3945/jn.116.231621.
Li YS, San Andres JV, Trenhaile-Grannemann MD, van Sambeek DM, Moore KC, Winkel SM, Fernando SC, Burkey TE, Miller PS. Effects of mannan oligosaccharides and Lactobacillus mucosae on growth performance, immune response, and gut health of weanling pigs challenged with Escherichia coli lipopolysaccharides. J Anim Sci 2021b;99(12). https://doi.org/10.1093/jas/skab286.
Liu B, Jian Z, Li Q, Li K, Wang Z, Liu L, Tang L, Yi X, Wang H, Li C, Gao T. Baicalein protects human melanocytes from H(2)O(2)-induced apoptosis via inhibiting mitochondria-dependent caspase activation and the p38 MAPK pathway. Free Radic Biol Med 2012;53(2):183−93. https://doi.org/10.1016/j.freeradbiomed.2012.04.015.
Liu F, Celi P, Cottrell JJ, Chauhan SS, Leury BJ, Dunshea FR. Effects of a short-term supranutritional selenium supplementation on redox balance, physiology and insulin-related metabolism in heat-stressed pigs. J Anim Physiol Anim Nutr 2018a;102(1):276−85. https://doi.org/10.1111/jpn.12689.
Liu F, Cottrell JJ, Furness JB, Rivera LR, Kelly FW, Wijesiriwardana U, Pustovit RV, Fothergill LJ, Bravo DM, Celi P, Leury BJ, Gabler NK, Dunshea FR. Selenium and vitamin E together improve intestinal epithelial barrier function and alleviate oxidative stress in heat-stressed pigs. Exp Physiol 2016;101(7):801−10. https://doi.org/10.1113/EP085746.

Liu F, Yin J, Du M, Yan P, Xu J, Zhu X, Yu J. Heat-stress-induced damage to porcine small intestinal epithelium associated with downregulation of epithelial growth factor signaling. J Anim Sci 2009;87(6):1941–9. https://doi.org/10.2527/jas.2008-1624.
Liu L, Chen D, Yu B, Yin H, Huang Z, Luo Y, Zheng P, Mao X, Yu J, Luo J, Yan H, He J. Fructooligosaccharides improve growth performance and intestinal epithelium function in weaned pigs exposed to enterotoxigenic Escherichia coli. Food Funct 2020;11(11):9599–612. https://doi.org/10.1039/d0fo01998d.
Liu P, Piao XS, Kim SW, Wang L, Shen YB, Lee HS, Li SY. Effects of chito-oligosaccharide supplementation on the growth performance, nutrient digestibility, intestinal morphology, and fecal shedding of Escherichia coli and Lactobacillus in weaning pigs. J Anim Sci 2008;86(10):2609–18. https://doi.org/10.2527/jas.2007-0668.
Liu Y, Espinosa CD, Abelilla JJ, Casas GA, Lagos LV, Lee SA, Kwon WB, Mathai JK, Navarro D, Jaworski NW, Stein HH. Non-antibiotic feed additives in diets for pigs: a review. Anim Nutr 2018b;4(2):113–25. https://doi.org/10.1016/j.aninu.2018.01.007.
Looft T, Allen HK. Collateral effects of antibiotics on mammalian gut microbiomes. Gut Microb 2012;3(5):463–7. https://doi.org/10.4161/gmic.21288.
Lopez-Colom P, Castillejos L, Rodriguez-Sorrento A, Puyalto M, Mallo JJ, Martin-Orue SM. Efficacy of medium-chain fatty acid salts distilled from coconut oil against two enteric pathogen challenges in weanling piglets. J Anim Sci Biotechnol 2019;10:89. https://doi.org/10.1186/s40104-019-0393-y.
Lordelo MM, Gaspar AM, Le Bellego L, Freire JP. Isoleucine and valine supplementation of a low-protein corn-wheat-soybean meal-based diet for piglets: growth performance and nitrogen balance. J Anim Sci 2008;86(11):2936–41. https://doi.org/10.2527/jas.2007-0222.
Lu H, Su S, Ajuwon KM. Butyrate supplementation to gestating sows and piglets induces muscle and adipose tissue oxidative genes and improves growth performance. J Anim Sci 2012;90(Suppl 4):430–2. https://doi.org/10.2527/jas.53817.
Lucy MC, Safranski TJ. Heat stress in pregnant sows: thermal responses and subsequent performance of sows and their offspring. Mol Reprod Dev 2017;84(9):946–56. https://doi.org/10.1002/mrd.22844.
Lugrin J, Rosenblatt-Velin N, Parapanov R, Liaudet L. The role of oxidative stress during inflammatory processes. Biol Chem 2014;395(2):203–30. https://doi.org/10.1515/hsz-2013-0241.
Lunney JK, Van Goor A, Walker KE, Hailstock T, Franklin J, Dai C. Importance of the pig as a human biomedical model. Sci Transl Med 2021;13(621):eabd5758. https://doi.org/10.1126/scitranslmed.abd5758.
Maher T, Sampson A, Goslawska M, Pangua-Irigaray C, Shafat A, Clegg ME. Food intake and satiety response after medium-chain triglycerides ingested as solid or liquid. Nutrients 2019;11(7). https://doi.org/10.3390/nu11071638.
Mao B, Gu J, Li D, Cui S, Zhao J, Zhang H, Chen W. Effects of different doses of fructooligosaccharides (FOS) on the composition of mice fecal microbiota, especially the Bifidobacterium composition. Nutrients 2018;10(8). https://doi.org/10.3390/nu10081105.
Mao X, Liu M, Tang J, Chen H, Chen D, Yu B, He J, Yu J, Zheng P. Dietary leucine supplementation improves the mucin production in the jejunal mucosa of the weaned pigs challenged by porcine rotavirus. PLoS One 2015;10(9):e0137380. https://doi.org/10.1371/journal.pone.0137380.
Mao X, Yang Q, Chen D, Yu B, He J. Benzoic acid used as food and feed additives can regulate gut functions. BioMed Res Int 2019;2019:5721585. https://doi.org/10.1155/2019/5721585.
Markowiak P, Slizewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients 2017;9(9). https://doi.org/10.3390/nu9091021.
Martinez-Miro S, Tecles F, Ramon M, Escribano D, Hernandez F, Madrid J, Orengo J, Martinez-Subiela S, Manteca X, Ceron JJ. Causes, consequences and biomarkers of stress in swine: an update. BMC Vet Res 2016;12(1):171. https://doi.org/10.1186/s12917-016-0791-8.
Mateo RD, Wu G, Moon HK, Carroll JA, Kim SW. Effects of dietary arginine supplementation during gestation and lactation on the performance of lactating primiparous sows and nursing piglets. J Anim Sci 2008;86(4):827–35. https://doi.org/10.2527/jas.2007-0371.
Matsui H, Imai T, Kondo M, Ban-Tokuda T, Yamada Y. Effects of the supplementation of a calcium soap containing medium-chain fatty acids on the fecal microbiota of pigs, lactating cows, and calves. Anim Sci J 2021;92(1):e13636. https://doi.org/10.1111/asj.13636.
Mayorga EJ, Kvidera SK, Seibert JT, Horst EA, Abuajamieh M, Al-Qaisi M, Lei S, Ross JW, Johnson CD, Kremer B, Ochoa L, Rhoads RP, Baumgard LH. Effects of dietary chromium propionate on growth performance, metabolism, and immune biomarkers in heat-stressed finishing pigs1. J Anim Sci 2019;97(3):1185–97. https://doi.org/10.1093/jas/sky484.
McCoy S, Gilliland SE. Isolation and characterization of Lactobacillus species having potential for use as probiotic cultures for dogs. J Food Sci 2007;72(3):M94–7. https://doi.org/10.1111/j.1750-3841.2007.00310.x.
McDonnell P, Figat S, O'Doherty JV. The effect of dietary laminarin and fucoidan in the diet of the weanling piglet on performance, selected faecal microbial populations and volatile fatty acid concentrations. Animal 2010;4(4):579–85. https://doi.org/10.1017/S1751731109991376.
Meissner F, Scheltema RA, Mollenkopf HJ, Mann M. Direct proteomic quantification of the secretome of activated immune cells. Science 2013;340(6131):475–8. https://doi.org/10.1126/science.1232578.
Meng Q, Guo T, Li G, Sun S, He S, Cheng B, Shi B, Shan A. Dietary resveratrol improves antioxidant status of sows and piglets and regulates antioxidant gene expression in placenta by Keap1-Nrf2 pathway and Sirt1. J Anim Sci Biotechnol 2018;9:34. https://doi.org/10.1186/s40104-018-0248-y.
Mennah-Govela YA, Cai H, Chu J, Kim K, Maborang MK, Sun W, Bornhorst GM. Buffering capacity of commercially available foods is influenced by composition and initial properties in the context of gastric digestion. Food Funct 2020;11(3):2255–67. https://doi.org/10.1039/c9fo03033f.
Mirzaei H, Raynes R, Longo VD. The conserved role of protein restriction in aging and disease. Curr Opin Clin Nutr Metab Care 2016;19(1):74–9. https://doi.org/10.1097/MCO.0000000000000239.
Modesto M, D"Aimmo MR, Stefanini I, Trevisi P, Filippi SD, Casini L, et al. A novel strategy to select Bifidobacterium strains and prebiotics as natural growth promoters in newly weaned pigs. Livest Sci 2009;122(2–3):248–58. https://doi.org/10.1016/j.livsci.2008.08.017.
Moeckel GW, Shadman R, Fogel JM, Sadrzadeh SM. Organic osmolytes betaine, sorbitol and inositol are potent inhibitors of erythrocyte membrane ATPases. Life Sci 2002;71(20):2413–24. https://doi.org/10.1016/s0024-3205(02)02035-0.
Mohammad MA, Molloy A, Fau - Scott J, Scott J, Fau - Hussein L, Hussein L. Plasma cobalamin and folate and their metabolic markers methylmalonic acid and total homocysteine among Egyptian children before and after nutritional supplementation with the probiotic bacteria Lactobacillus acidophilus in yoghurt matrix. 2006 (0963-7486 (Print)).
Morales A, Gómez T, Villalobos YD, Bernal H, Htoo JK, González-Vega JC, Espinoza S, Yáñez J, Cervantes M. Dietary protein-bound or free amino acids differently affect intestinal morphology, gene expression of amino acid transporters, and serum amino acids of pigs exposed to heat stress. J Anim Sci 2020;98(3). https://doi.org/10.1093/jas/skaa056.
Morgan MJ, Liu ZG. Crosstalk of reactive oxygen species and NF-kappaB signaling. Cell Res 2011;21(1):103–15. https://doi.org/10.1038/cr.2010.178.
Motohashi H, Yamamoto M. Nrf2-Keap1 defines a physiologically important stress response mechanism. Trends Mol Med 2004;10(11):549–57. https://doi.org/10.1016/j.molmed.2004.09.003.
Myatt L, Cui X. Oxidative stress in the placenta. Histochem Cell Biol 2004;122(4):369–82. https://doi.org/10.1007/s00418-004-0677-x.
Nandi D, Patra RC, Swarup D. Effect of cysteine, methionine, ascorbic acid and thiamine on arsenic-induced oxidative stress and biochemical alterations in rats. Toxicology 2005;211(1–2):26–35. https://doi.org/10.1016/j.tox.2005.02.013.
Nie C, He T, Zhang W, Zhang G, Ma X. Branched chain amino acids: beyond nutrition metabolism. Int J Mol Sci 2018;19(4). https://doi.org/10.3390/ijms19040954.
Niu Y, He J, Ahmad H, Shen M, Zhao Y, Gan Z, et al. Dietary curcumin supplementation increases antioxidant capacity, upregulates Nrf2 and Hmox1 levels in the liver of piglet model with intrauterine growth retardation. Nutrients 2019;11(12):2978. https://doi.org/10.3390/nu11122978.
Nochta I, Tuboly T, Halas V, Babinszky L. Effect of different levels of mannan-oligosaccharide supplementation on some immunological variables in weaned piglets. J Anim Physiol Anim Nutr 2009;93(4):496–504. https://doi.org/10.1111/j.1439-0396.2008.00835.x.
Novak S, Paradis F, Patterson JL, Pasternak JA, Oxtoby K, Moore HS, Hahn M, Dyck MK, Dixon WT, Foxcroft GR. Temporal candidate gene expression in the sow placenta and embryo during early gestation and effect of maternal Progenos supplementation on embryonic and placental development. Reprod Fertil Dev 2012;24(4):550–8. https://doi.org/10.1071/rd10312.
O'Shea CJ, O'Doherty JV, Callanan JJ, Doyle D, Thornton K, Sweeney T. The effect of algal polysaccharides laminarin and fucoidan on colonic pathology, cytokine gene expression and Enterobacteriaceae in a dextran sodium sulfate-challenged porcine model. J Nutr Sci 2016;5:e15. https://doi.org/10.1017/jns.2016.4.
Oliviero C, Heinonen M, Valros A, Peltoniemi O. Environmental and sow-related factors affecting the duration of farrowing. Anim Reprod Sci 2010;119(1–2):85–91. https://doi.org/10.1016/j.anireprosci.2009.12.009.
Parihar A, Pandita V, Khan R. 3D printed human organoids: high throughput system for drug screening and testing in current COVID-19 pandemic. Biotechnol Bioeng 2022;119(10):2669–88. https://doi.org/10.1002/bit.28166.
Partanen KH, Mroz Z. Organic acids for performance enhancement in pig diets. Nutr Res Rev 1999;12(1):117–45. https://doi.org/10.1079/095442299108728884.
Pearce Nathan C, Harris Amanda, Gabler, Ross Nicholas K, Jason W. Effects of heat stress on energetic metabolism in growing pigs. Faseb J 2010;25(2):644–55.
Pearson G, Robinson F, Beers Gibson T, Xu BE, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev 2001;22(2):153–83. https://doi.org/10.1210/edrv.22.2.0428.
Peeters E, Driessen B, Steegmans R, Henot D, Geers R. Effect of supplemental tryptophan, vitamin E, and a herbal product on responses by pigs to vibration. J Anim Sci 2004;82(8):2410–20. https://doi.org/10.2527/2004.8282410x.
Peeters E, Geers R. Influence of provision of toys during transport and lairage on stress responses and meat quality of pigs. Anim Sci 2006;82(5):591–5. https://doi.org/10.1079/ASC200686.
Peltoniemi O, Bjorkman S, Oliviero C. Parturition effects on reproductive health in the gilt and sow. Reprod Domest Anim 2016;51(Suppl 2):36–47. https://doi.org/10.1111/rda.12798.
Peng M, Wang Z, Peng S, Zhang M, Duan Y, Li F, Shi S, Yang Q, Zhang C. Dietary supplementation with the extract from Eucommia ulmoides leaves changed epithelial restitution and gut microbial community and composition of weanling piglets. PLoS One 2019;14(9):e0223002. https://doi.org/10.1371/journal.pone.0223002.

Perez-Cobas AE, Gosalbes MJ, Friedrichs A, Knecht H, Artacho A, Eismann K, Otto W, Rojo D, Bargiela R, von Bergen M, Neulinger SC, Daumer C, Heinsen FA, Latorre A, Barbas C, Seifert J, dos Santos VM, Ott SJ, Ferrer M, Moya A. Gut microbiota disturbance during antibiotic therapy: a multi-omic approach. Gut 2013;62(11):1591–601. https://doi.org/10.1136/gutjnl-2012-303184.
Pi D, Liu Y, Shi H, Li S, Odle J, Lin X, Zhu H, Chen F, Hou Y, Leng W. Dietary supplementation of aspartate enhances intestinal integrity and energy status in weanling piglets after lipopolysaccharide challenge. J Nutr Biochem 2014;25(4): 456–62. https://doi.org/10.1016/j.jnutbio.2013.12.006.
Pineiro M, Asp N-G, Reid G, Macfarlane S, Morelli L, Brunser O, Tuohy K. FAO technical meeting on prebiotics. J Clin Gastroenterol 2008;42:S156–9. https://doi.org/10.1097/MCG.0b013e31817f184e.
Pluske JR, Hampson DJ, Williams IH. Factors influencing the structure and function of the small intestine in the weaned pig: a review. Livest Prod Sci 1997;51(1–3): 215–36. https://doi.org/10.1016/S0301-6226(97)00057-2.
Pluske JR, Pethick DW, Hopwood DE, Hampson DJ. Nutritional influences on some major enteric bacterial diseases of pig. Nutr Res Rev 2002;15(2):333–71. https://doi.org/10.1079/nrr200242.
Pourabedin M, Xu Z, Baurhoo B, Chevaux E, Zhao X. Effects of mannan oligosaccharide and virginiamycin on the cecal microbial community and intestinal morphology of chickens raised under suboptimal conditions. Can J Microbiol 2014;60(5):255–66. https://doi.org/10.1139/cjm-2013-0899.
Pu Y, Li S, Xiong H, Zhang X, Wang Y, Du H. Iron promotes intestinal development in neonatal piglets. Nutrients 2018;10(6). https://doi.org/10.3390/nu10060726.
Quiniou N, Dubois S, Noblet J. Voluntary feed intake and feeding behaviour of group-housed growing pigs are affected by ambient temperature and body weight. Livest Prod Sci 2000;63(3):245–53.
Radwan RR, Karam HM. Resveratrol attenuates intestinal injury in irradiated rats via PI3K/Akt/mTOR signaling pathway. Environ Toxicol 2020;35(2):223–30. https://doi.org/10.1002/tox.22859.
Raingeaud J, Whitmarsh AJ, Barrett T, Derijard B, Davis RJ. MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. Mol Cell Biol 1996;16(3):1247–55. https://doi.org/10.1128/MCB.16.3.1247.
Ramirez BC, Hayes MD, Condotta I, Leonard SM. Impact of housing environment and management on pre-/post-weaning piglet productivity. J Anim Sci 2022;100(6). https://doi.org/10.1093/jas/skac142.
Reilly P, O'Doherty JV, Pierce KM, Callan JJ, O'Sullivan JT, Sweeney T. The effects of seaweed extract inclusion on gut morphology, selected intestinal microbiota, nutrient digestibility, volatile fatty acid concentrations and the immune status of the weaned pig. Animal 2008;2(10):1465–73. https://doi.org/10.1017/S1751731108002711.
Ren C, Zhou Q, Guan W, Lin X, Wang Y, Song H, Zhang Y. Immune response of piglets receiving mixture of formic and propionic acid alone or with either capric acid or Bacillus licheniformis after Escherichia coli challenge. BioMed Res Int 2019;2019:6416187. https://doi.org/10.1155/2019/6416187.
Ren M, Liu C, Zeng X, Yue L, Mao X, Qiao S, Wang J. Amino acids modulates the intestinal proteome associated with immune and stress response in weaning pig. Mol Biol Rep 2014a;41(6):3611–20. https://doi.org/10.1007/s11033-014-3225-3.
Ren W, Duan J, Yin J, Liu G, Cao Z, Xiong X, Chen S, Li T, Yin Y, Hou Y, Wu G. Dietary L-glutamine supplementation modulates microbial community and activates innate immunity in the mouse intestine. Amino Acids 2014b;46(10):2403–13. https://doi.org/10.1007/s00726-014-1793-0.
Rezaei R, Knabe DA, Tekwe CD, Dahanayaka S, Ficken MD, Fielder SE, Eide SJ, Lovering SL, Wu G. Dietary supplementation with monosodium glutamate is safe and improves growth performance in postweaning pigs. Amino Acids 2013;44(3):911–23. https://doi.org/10.1007/s00726-012-1420-x.
Rhoads RP, Baumgard LH, Suagee JK, Sanders SR. Nutritional interventions to alleviate the negative consequences of heat stress. Adv Nutr 2013;4(3):267–76. https://doi.org/10.3945/an.112.003376.
Rieu I, Balage M, Sornet C, Giraudet C, Pujos E, Grizard J, Mosoni L, Dardevet D. Leucine supplementation improves muscle protein synthesis in elderly men independently of hyperaminoacidaemia. J Physiol 2006;575(Pt 1):305–15. https://doi.org/10.1113/jphysiol.2006.110742.
Rio D.D., Stewart A.J., Pellegrini N. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. Nutr Metabol Cardiovasc Dis 2005;15:316–328 " Nutrition Metabolism and Cardiovascular Diseases 15(4): 316-328. doi:10.1016/j.numecd.2005.05.003
Rist VT, Weiss E, Eklund M, Mosenthin R. Impact of dietary protein on microbiota composition and activity in the gastrointestinal tract of piglets in relation to gut health: a review. Animal 2013;7(7):1067–78. https://doi.org/10.1017/s1751731113000062.
Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Leotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck AM, Meheust A. Prebiotic effects: metabolic and health benefits. Br J Nutr 2010;104(Suppl 2):S1–63. https://doi.org/10.1017/S0007114510003363.
Rosignoli P, Fabiani R, De Bartolomeo A, Spinozzi F, Agea E, Pelli MA, Morozzi G. Protective activity of butyrate on hydrogen peroxide-induced DNA damage in isolated human colonocytes and HT29 tumour cells. Carcinogenesis 2001;22(10):1675–80. https://doi.org/10.1093/carcin/22.10.1675.
Ross JW, Hale BJ, Gabler NK, Rhoads RP, Keating AF, Baumgard LH. Physiological consequences of heat stress in pigs. Anim Prod Sci 2015;55(12). https://doi.org/10.1071/an15267.
Sabio G, Davis RJ. TNF and MAP kinase signalling pathways. Semin Immunol 2014;26(3):237–45. https://doi.org/10.1016/j.smim.2014.02.009.
Santana-Gálvez J, Cisneros-Zevallos L, Jacobo-Velázquez DA. Chlorogenic acid: recent advances on its dual role as a food additive and a nutraceutical against metabolic syndrome. Molecules 2017;22(3). https://doi.org/10.3390/molecules22030358.
Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci 2016;39(11): 763–81. https://doi.org/10.1016/j.tins.2016.09.002.
Schokker D, Fledderus J, Jansen R, Vastenhouw SA, de Bree FM, Smits MA, Jansman A. Supplementation of fructooligosaccharides to suckling piglets affects intestinal microbiota colonization and immune development. J Anim Sci 2018;96(6):2139–53. https://doi.org/10.1093/jas/sky110.
Shadmehr S, Fatemi Tabatabaei SR, Hosseinifar S, Tabandeh MR, Amiri A. Attenuation of heat stress-induced spermatogenesis complications by betaine in mice. Theriogenology 2018;106:117–26. https://doi.org/10.1016/j.theriogenology.2017.10.008.
Shen YB, Weaver AC, Kim SW. Effect of feed grade L-methionine on growth performance and gut health in nursery pigs compared with conventional DL-methionine. J Anim Sci 2014;92(12):5530–9. https://doi.org/10.2527/jas.2014-7830.
Shi B, Su Y, Chang S, Sun Y, Meng X, Shan A. Vitamin C protects piglet liver against zearalenone-induced oxidative stress by modulating expression of nuclear receptors PXR and CAR and their target genes. Food Funct 2017;8(10):3675–87. https://doi.org/10.1039/c7fo01301a.
Shin D, Chang SY, Bogere P, Won K, Choi JY, Choi YJ, Lee HK, Hur J, Park BY, Kim Y, Heo J. Beneficial roles of probiotics on the modulation of gut microbiota and immune response in pigs. PLoS One 2019;14(8):e0220843. https://doi.org/10.1371/journal.pone.0220843.
Shin JH, Jeong JY, Jin Y, Kim ID, Lee JK. p38beta MAPK affords cytoprotection against oxidative stress-induced astrocyte apoptosis via induction of alphaB-crystallin and its anti-apoptotic function. Neurosci Lett 2011;501(3):132–7. https://doi.org/10.1016/j.neulet.2011.06.061.
Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. Mech Ageing Dev 2005;126(9):987–1002. https://doi.org/10.1016/j.mad.2005.03.019.
Singboottra P. Agglutination of type-1 fimbrial bacteria by different yeast cell Wall. Raleigh, NC, USA: North Carolina State University; 2005.
Singh SP, Jadaun JS, Narnoliya LK, Pandey A. Prebiotic oligosaccharides: special focus on fructooligosaccharides, its biosynthesis and bioactivity. Appl Biochem Biotechnol 2017;183(2):613–35. https://doi.org/10.1007/s12010-017-2605-2.
Singla AK, Chawla M. Chitosan: some pharmaceutical and biological aspects–an update. J Pharm Pharmacol 2001;53(8):1047–67. https://doi.org/10.1211/0022357011776441.
Sivropoulou A, Papanikolaou E, Nikolaou C, Kokkini S, Lanaras T, Arsenakis M. Antimicrobial and cytotoxic activities of origanum essential oils. J Agric Food Chem 1996:44. https://doi.org/10.1021/JF950540T.
Sosa V, Moline T, Somoza R, Paciucci R, Kondoh H, Me LL. Oxidative stress and cancer: an overview. Ageing Res Rev 2013;12(1):376–90. https://doi.org/10.1016/j.arr.2012.10.004.
Splichalova A, Jenistova V, Splichalova Z, Splichal I. Colonization of preterm gnotobiotic piglets with probiotic Lactobacillus rhamnosus GG and its interference with Salmonella Typhimurium. Clin Exp Immunol 2019;195(3):381–94. https://doi.org/10.1111/cei.13236.
Srinongkote S, Smriga M, Nakagawa K, Toride Y. A diet fortified with L-lysine and L-arginine reduces plasma cortisol and blocks anxiogenic response to transportation in pigs. Nutr Neurosci 2003;6(5):283–9. https://doi.org/10.1080/10284150310001614661.
St-Onge MP, Jones PJ. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J Nutr 2002;132(3):329–32. https://doi.org/10.1093/jn/132.3.329.
Su W, Zhang H, Ying Z, Li Y, Zhou L, Wang F, Zhang L, Wang T. Effects of dietary L-methionine supplementation on intestinal integrity and oxidative status in intrauterine growth-retarded weanling piglets. Eur J Nutr 2018;57(8):2735–45. https://doi.org/10.1007/s00394-017-1539-3.
Suiryanrayna MV, Ramana JV. A review of the effects of dietary organic acids fed to swine. J Anim Sci Biotechnol 2015;6:45. https://doi.org/10.1186/s40104-015-0042-z.
Sumien N, Cunningham JT, Davis DL, Engelland R, Fadeyibi O, Farmer GE, Mabry S, Mensah-Kane P, Trinh OTP, Vann PH, Wilson EN, Cunningham RL. Neurodegenerative disease: roles for sex, hormones, and oxidative stress. Endocrinology 2021;162(11). https://doi.org/10.1210/endocr/bqab185.
Sun K, Wang X, Zhang X, Shi X, Gong D. The antagonistic effect of melatonin on TBBPA-induced apoptosis and necroptosis via PTEN/PI3K/AKT signaling pathway in swine testis cells. Environ Toxicol 2022;37(9):2281–90. https://doi.org/10.1002/tox.23595.
Sun L, Gong M, Lv X, Huang Z, Gu Y, Li J, Du G, Liu L. Current advance in biological production of short-chain organic acid. Appl Microbiol Biotechnol 2020a;104(21):9109–24. https://doi.org/10.1007/s00253-020-10917-0.
Sun W, Sun J, Li M, Xu Q, Zhang X, Tang Z, Chen J, Zhen J, Sun Z. The effects of dietary sodium butyrate supplementation on the growth performance, carcass traits

and intestinal microbiota of growing-finishing pigs. J Appl Microbiol 2020b;128(6):1613–23. https://doi.org/10.1111/jam.14612.
Supanji, Shimomachi M, Hasan MZ, Kawaichi M, Oka C. HtrA1 is induced by oxidative stress and enhances cell senescence through p38 MAPK pathway. Exp Eye Res 2013;112:79–92. https://doi.org/10.1016/j.exer.2013.04.013.
Surya S, Salam AD, Tomy DV, Carla B, Kumar RA, Sunil C. Diabetes mellitus and medicinal plants-a review. Asian Pacific Journal of Tropical Disease 2014;4(5): 337–47.
Tako E, Glahn RP, Welch RM, Lei X, Yasuda K, Miller DD. Dietary inulin affects the expression of intestinal enterocyte iron transporters, receptors and storage protein and alters the microbiota in the pig intestine. Br J Nutr 2008;99(3): 472–80. https://doi.org/10.1017/S0007114507825128.
Tan B, Li XG, Kong X, Huang R, Ruan Z, Yao K, Deng Z, Xie M, Shinzato I, Yin Y, Wu G. Dietary L-arginine supplementation enhances the immune status in early-weaned piglets. Amino Acids 2009;37(2):323–31. https://doi.org/10.1007/s00726-008-0155-1.
Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. Adv Immunol 2014;121:91–119. https://doi.org/10.1016/B978-0-12-800100-4.00003-9.
Tanaka T, Imai Y, Kumagae N, Sato S. The effect of feeding lactic acid to Salmonella typhimurium experimentally infected swine. J Vet Med Sci 2010;72(7):827–31. https://doi.org/10.1292/jvms.09-0490.
Tang W, Wu J, Jin S, He L, Lin Q, Luo F, He X, Feng Y, He B, Bing P, Li T, Yin Y. Glutamate and aspartate alleviate testicular/epididymal oxidative stress by supporting antioxidant enzymes and immune defense systems in boars. Sci China Life Sci 2020;63(1):116–24. https://doi.org/10.1007/s11427-018-9492-8.
Tang X, Liu H, Yang S, Li Z, Zhong J, Fang R. Epidermal growth factor and intestinal barrier function. Mediat Inflamm 2016;2016:1927348. https://doi.org/10.1155/2016/1927348.
Tang X, Xiong K, Fang R, Li M. Weaning stress and intestinal health of piglets: a review. Front Immunol 2022;13:1042778. https://doi.org/10.3389/fimmu.2022.1042778.
Tao Y, Drabik KA, Waypa TS, Musch MW, Alverdy JC, Schneewind O, Chang EB, Petrof EO. Soluble factors from Lactobacillus GG activate MAPKs and induce cytoprotective heat shock proteins in intestinal epithelial cells. Am J Physiol Cell Physiol 2006;290(4):C1018–30. https://doi.org/10.1152/ajpcell.00131.2005.
Tarrant PJV. The effects of handling, transport, slaughter and chilling on meat quality and yield in pigs–a review. 1989.
Tian R, Geng Y, Yang Y, Seim I, Yang G. Oxidative stress drives divergent evolution of the glutathione peroxidase (GPX) gene family in mammals. Integr Zool 2021;6(5):696–711. https://doi.org/10.1111/1749-4877.12521.
Tizard IR, Carpenter RH, McAnalley BH, Kemp MC. The biological activities of mannans and related complex carbohydrates. Mol Biother 1989;1(6):290–6.
Tvrzicka E, Kremmyda LS, Stankova B, Zak A. Fatty acids as biocompounds: their role in human metabolism, health and disease–a review. Part 1: classification, dietary sources and biological functions. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011;155(2):117–30. https://doi.org/10.5507/bp.2011.038.
Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Socci ND, van den Brink MR, Kamboj M, Pamer EG. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 2010;120(12):4332–41. https://doi.org/10.1172/JCI43918.
Upadhaya SD, Kim IH. The impact of weaning stress on gut health and the mechanistic aspects of several feed additives contributing to improved gut health function in weanling piglets-A review. Animals (Basel) 2021;11(8). https://doi.org/10.3390/ani11082418.
Vallabhapurapu S, Karin M. Regulation and function of NF-kappaB transcription factors in the immune system. Annu Rev Immunol 2009;27:693–733. https://doi.org/10.1146/annurev.immunol.021908.132641.
Vokou D, Kokkini S, Bessiere J-M. Geographic variation of Greek oregano (Origanum vulgare ssp. hirtum) essential oils. Biochemical Systematics and Ecology 1993;21(2):287–95. https://doi.org/10.1016/0305-1978(93)90047-U.
Walsh AM, Sweeney T, O'Shea CJ, Doyle DN, O'Doherty JV. Effect of dietary laminarin and fucoidan on selected microbiota, intestinal morphology and immune status of the newly weaned pig. Br J Nutr 2013;110(9):1630–8. https://doi.org/10.1017/S0007114513000834.
Wang AN, Cai CJ, Zeng XF, Zhang FR, Zhang GL, Thacker PA, Wang JJ, Qiao SY. Dietary supplementation with Lactobacillus fermentum I5007 improves the antioxidative activity of weanling piglets challenged with diquat. J Appl Microbiol 2013a;114(6):1582–91. https://doi.org/10.1111/jam.12188.
Wang AN, Yi XW, Yu HF, Dong B, Qiao SY. Free radical scavenging activity of Lactobacillus fermentum in vitro and its antioxidative effect on growing-finishing pigs. J Appl Microbiol 2009;107(4):1140–8. https://doi.org/10.1111/j.1365-2672.2009.04294.x.
Wang DD, Pan WJ, Mehmood S, Cheng XD, Chen Y. Polysaccharide isolated from Sarcodon aspratus induces RAW264.7 activity via TLR4-mediated NF-kappaB and MAPK signaling pathways. Int J Biol Macromol 2018a;120(Pt A):1039–47. https://doi.org/10.1016/j.ijbiomac.2018.08.147.
Wang J, Li ZX, Yang DD, Liu PQ, Wang ZQ, Zeng YQ, Chen W. Diquat determines a deregulation of lncRNA and mRNA expression in the liver of postweaned piglets. Oxid Med Cell Longev 2019a;2019:9148535. https://doi.org/10.1155/2019/9148535.
Wang J, Wang S, Liu H, Zhang D, Wang Y, Ji H. Effects of oligosaccharides on the growth and stress tolerance of Lactobacillus plantarum ZLP001 in vitro, and the potential synbiotic effects of L. plantarum ZLP001 and fructo-oligosaccharide in post-weaning piglets1. J Anim Sci 2019b;97(11):4588–97. https://doi.org/10.1093/jas/skz254.
Wang L, Hou Y, Yi D, Li Y, Ding B, Zhu H, Liu J, Xiao H, Wu G. Dietary supplementation with glutamate precursor α-ketoglutarate attenuates lipopolysaccharide-induced liver injury in young pigs. Amino Acids 2015;47(7):1309–18. https://doi.org/10.1007/s00726-015-1966-5.
Wang L, Liu Q, Chen Y, Zheng X, Wang C, Qi Y, Dong Y, Xiao Y, Chen C, Chen T, Huang Q, Zhai Z, Long C, Yang H, Li J, Wang L, Zhang G, Liao P, Liu YX, Huang P, Huang J, Wang Q, Chu H, Yin J, Yin Y. Antioxidant potential of Pediococcus pentosaceus strains from the sow milk bacterial collection in weaned piglets. Microbiome 2022;10(1):83. https://doi.org/10.1186/s40168-022-01278-z.
Wang L, Zou L, Li J, Yang H, Yin Y. Effect of dietary folate level on organ weight, digesta pH, short-chain fatty acid concentration, and intestinal microbiota of weaned piglets. J Anim Sci 2021;99(1). https://doi.org/10.1093/jas/skab015.
Wang LX, Liu K, Gao DW, Hao JK. Protective effects of two Lactobacillus plantarum strains in hyperlipidemic mice. World J Gastroenterol 2013b;19(20):3150–6. https://doi.org/10.3748/wjg.v19.i20.3150.
Wang P, Lu Z, He M, Shi B, Lei X, Shan A. The effects of endoplasmic-reticulum-resident selenoproteins in a nonalcoholic fatty liver disease pig model induced by a high-fat diet. Nutrients 2020a;12(3). https://doi.org/10.3390/nu12030692.
Wang P, Yao J, Deng L, Yang X, Luo W, Zhou W. Pretreatment with antibiotics impairs Th17-mediated antifungal immunity in newborn rats. Inflammation 2020b;43(6):2202–8. https://doi.org/10.1007/s10753-020-01287-w.
Wang X, Jiang G, Kebreab E, Yu Q, Li J, Zhang X, He H, Fang R, Dai Q. Effects of dietary grape seed polyphenols supplementation during late gestation and lactation on antioxidant status in serum and immunoglobulin content in colostrum of multiparous sows1. J Anim Sci 2019c;97(6):2515–23. https://doi.org/10.1093/jas/skz128.
Wang XY, Zhao TQ, Xu DP, Zhang X, Ji CJ, Zhang DL. The influence of porcine epidemic diarrhea virus on pig small intestine mucosal epithelial cell function. Arch Virol 2019d;164(1):83–90. https://doi.org/10.1007/s00705-018-4061-x.
Wang Y, Tang JW, Ma WQ, Feng J, Feng J. Dietary zinc glycine chelate on growth performance, tissue mineral concentrations, and serum enzyme activity in weanling piglets. Biol Trace Elem Res 2010;133(3):325–34. https://doi.org/10.1007/s12011-009-8437-3.
Wang Y, Wu Y, Wang Y, Fu A, Gong L, Li W, et al. Bacillus amyloliquefaciens SC06 alleviates the oxidative stress of IPEC-1 via modulating Nrf2/Keap1 signaling pathway and decreasing ROS production. Appl Microbiol Biotechnol 2017;101(7):3015–26.
Wang Y, Wu Y, Wang Y, Xu H, Mei X, Yu D, Wang Y, Li W. Antioxidant properties of probiotic bacteria. Nutrients 2017;9(5). https://doi.org/10.3390/nu9050521.
Wang Y, Zhou J, Wang G, Cai S, Zeng X, Qiao S. Advances in low-protein diets for swine. J Anim Sci Biotechnol 2018b;9:60. https://doi.org/10.1186/s40104-018-0276-7.
Wang YS, Zhou P, Liu H, Li S, Zhao Y, Deng K, Cao DD, Che LQ, Fang ZF, Xu SY, Lin Y, Feng B, Li J, Wu D. Effects of inulin supplementation in low- or high-fat diets on reproductive performance of sows and antioxidant defence capacity in sows and offspring. Reprod Domest Anim 2016;51(4):492–500. https://doi.org/10.1111/rda.12707.
Wang YY, Sun SP, Zhu HS, Jiao XQ, Zhong K, Guo YJ, Zha GM, Han LQ, Yang GY, Li HP. GABA regulates the proliferation and apoptosis of MAC-T cells through the LPS-induced TLR4 signaling pathway. Res Vet Sci 2018c;118:395–402. https://doi.org/10.1016/j.rvsc.2018.04.004.
Wen X, Wang L, Zheng C, Yang X, Ma X, Wu Y, Chen Z, Jiang Z. Fecal scores and microbial metabolites in weaned piglets fed different protein sources and levels. Anim Nutr 2018;4(1):31–6. https://doi.org/10.1016/j.aninu.2017.10.006.
Wen Z-S, Lu J-J, Zou X-T. Effects of sodium butyrate on the intestinal morphology and DNA-binding activity of intestinal nuclear factor-κb in weanling pigs. J Anim Vet Adv 2012;11:814–21. https://doi.org/10.3923/javaa.2012.814.821.
Wessels AG, Kluge H, Mielenz N, Corrent E, Bartelt J, Stangl GI. Estimation of the leucine and histidine requirements for piglets fed a low-protein diet. Animal 2016;10(11):1803–11. https://doi.org/10.1017/S1751731116000823.
Westrom B, Arevalo Sureda E, Pierzynowska K, Pierzynowski SG, Perez-Cano FJ. The immature gut barrier and its importance in establishing immunity in newborn mammals. Front Immunol 2020;11:1153. https://doi.org/10.3389/fimmu.2020.01153.
Windey K, De Preter V, Verbeke K. Relevance of protein fermentation to gut health. Mol Nutr Food Res 2012;56(1):184–96. https://doi.org/10.1002/mnfr.201100542.
Wolever TM, Brighenti F, Royall D, Jenkins AL, Jenkins DJ. Effect of rectal infusion of short chain fatty acids in human subjects. Am J Gastroenterol 1989;84(9): 1027–33.
Wolter BF, Ellis M, Corrigan BP, DeDecker JM, Curtis SE, Parr EN, Webel DM. Impact of early postweaning growth rate as affected by diet complexity and space allocation on subsequent growth performance of pigs in a wean-to-finish production system. J Anim Sci 2003;81(2):353–9. https://doi.org/10.2527/2003.812353x.
Wu G. Amino acids: metabolism, functions, and nutrition. Amino Acids 2009;37(1): 1–17. https://doi.org/10.1007/s00726-009-0269-0.
Wu G. Functional amino acids in growth, reproduction, and health. Adv Nutr 2010;1(1):31–7. https://doi.org/10.3945/an.110.1008.
Wu G. Functional amino acids in nutrition and health. Amino Acids 2013;45(3): 407–11. https://doi.org/10.1007/s00726-013-1500-6.

Wu G. Dietary requirements of synthesizable amino acids by animals: a paradigm shift in protein nutrition. J Anim Sci Biotechnol 2014;5(1):34. https://doi.org/10.1186/2049-1891-5-34.
Wu G, Bazer FW, Davis TA, Jaeger LA, Johnson GA, Kim SW, Knabe DA, Meininger CJ, Spencer TE, Yin Y-L. Important roles for the arginine family of amino acids in swine nutrition and production. Livest Sci 2007;112(1–2):8–22. https://doi.org/10.1016/j.livsci.2007.07.003.
Wu G, Bazer FW, Johnson GA, Hou Y. BOARD-INVITED review: arginine nutrition and metabolism in growing, gestating, and lactating swine. J Anim Sci 2018;96(12):5035–51. https://doi.org/10.1093/jas/sky377.
Wu G, Bazer FW, Johnson GA, Knabe DA, Burghardt RC, Spencer TE, Li XL, Wang JJ. Triennial Growth Symposium: important roles for L-glutamine in swine nutrition and production. J Anim Sci 2011;89(7):2017–30. https://doi.org/10.2527/jas.2010-3614.
Wu L, Liao P, He L, Feng Z, Ren W, Yin J, Duan J, Li T, Yin Y. Dietary L-arginine supplementation protects weanling pigs from deoxynivalenol-induced toxicity. Toxins 2015;7(4):1341–54. https://doi.org/10.3390/toxins7041341.
Xia B, Meng Q, Feng X, Tang X, Jia A, Feng J, Zhang S, Zhang H. Probing the molecular regulation of lipopolysaccharide stress in piglet liver by comparative proteomics analysis. Electrophoresis 2018;39(18):2321–31. https://doi.org/10.1002/elps.201700467.
Xia Y, Chen S, Zhao Y, Chen S, Huang R, Zhu G, Yin Y, Ren W, Deng J. GABA attenuates ETEC-induced intestinal epithelial cell apoptosis involving GABAAR signaling and the AMPK-autophagy pathway. Food Funct 2019;10(11):7509–22. https://doi.org/10.1039/c9fo01863h.
Xiao D, Wang Y, Liu G, He J, Qiu W, Hu X, Feng Z, Ran M, Nyachoti CM, Kim SW, Tang Z, Yin Y. Effects of chitosan on intestinal inflammation in weaned pigs challenged by enterotoxigenic Escherichia coli. PLoS One 2014;9(8):e104192. https://doi.org/10.1371/journal.pone.0104192.
Xie C, Wu X, Long C, Wang Q, Fan Z, Li S, Yin Y. Chitosan oligosaccharide affects antioxidant defense capacity and placental amino acids transport of sows. BMC Vet Res 2016;12(1):243. https://doi.org/10.1186/s12917-016-0872-8.
Xiong W, Huang J, Li X, Zhang Z, Jin M, Wang J, Xu Y, Wang Z. Icariin and its phosphorylated derivatives alleviate intestinal epithelial barrier disruption caused by enterotoxigenic Escherichia coli through modulate p38 MAPK in vivo and in vitro. Faseb J 2020;34(1):1783–801. https://doi.org/10.1096/fj.201902265R.
Xu J, Chen X, Yu S, Su Y, Zhu W. Effects of early intervention with sodium butyrate on gut microbiota and the expression of inflammatory cytokines in neonatal piglets. PLoS One 2016;11(9):e0162461. https://doi.org/10.1371/journal.pone.0162461.
Yan Y, Zhou X, Guo K, Zhou F, Yang H. Chlorogenic acid protects against indomethacin-induced inflammation and mucosa damage by decreasing bacteroides-derived LPS. Front Immunol 2020;11:1125. https://doi.org/10.3389/fimmu.2020.01125.
Yang B, Xu B, Zhao H, Wang YB, Zhang J, Li CW, Wu Q, Cao YK, Li Y, Cao F. Dioscin protects against coronary heart disease by reducing oxidative stress and inflammation via Sirt1/Nrf2 and p38 MAPK pathways. Mol Med Rep 2018a;18(1):973–80. https://doi.org/10.3892/mmr.2018.9024.
Yang CM, Ferket PR, Hong QH, Zhou J, Cao GT, Zhou L, Chen AG. Effect of chito-oligosaccharide on growth performance, intestinal barrier function, intestinal morphology and cecal microflora in weaned pigs. J Anim Sci 2012;90(8):2671–6. https://doi.org/10.2527/jas.2011-4699.
Yang F, Luan B, Sun Z, Yang C, Yu Z, Li X. Application of chitooligosaccharides as antioxidants in beer to improve the flavour stability by protecting against beer staling during storage. Biotechnol Lett 2017;39(2):305–10. https://doi.org/10.1007/s10529-016-2248-3.
Yang J, Qiu Y, Hu S, Zhu C, Wang L, Wen X, Yang X, Jiang Z. Lactobacillus plantarum inhibited the inflammatory response induced by enterotoxigenic Escherichia coli K88 via modulating MAPK and NF-kappaB signalling in intestinal porcine epithelial cells. J Appl Microbiol 2021a;130(5):1684–94. https://doi.org/10.1111/jam.14835.
Yang J, Wang C, Huang K, Zhang M, Wang J, Pan X. Compound Lactobacillus sp. administration ameliorates stress and body growth through gut microbiota optimization on weaning piglets. Appl Microbiol Biotechnol 2020;104(15):6749–65. https://doi.org/10.1007/s00253-020-10727-4.
Yang P, Wang HK, Li LX, Ma YX. The strategies for the supplementation of vitamins and trace minerals in pig production: surveying major producers in China. Anim Biosci 2021b;34(8):1350–64. https://doi.org/10.5713/ajas.20.0521.
Yang WR, Liao TT, Bao ZQ, Zhou CQ, Luo HY, Lu C, Pan MH, Wang XZ. Role of AMPK in the expression of tight junction proteins in heat-treated porcine Sertoli cells. Theriogenology 2018b;121:42–52. https://doi.org/10.1016/j.theriogenology.2018.08.005.
Yang Y, Chen N, Sun L, Zhang Y, Wu Y, Wang Y, Liao X, Mi J. Short-term cold stress can reduce the abundance of antibiotic resistance genes in the cecum and feces in a pig model. J Hazard Mater 2021c;416:125868. https://doi.org/10.1016/j.jhazmat.2021.125868.
Yazbeck R, Lindsay RJ, Geier MS, Butler RN, Howarth GS. Prebiotics fructo-, galacto-, and mannan-oligosaccharide do not protect against 5-fluorouracil-induced intestinal mucositis in rats. J Nutr 2019;149(12):2164–73. https://doi.org/10.1093/jn/nxz192.
Yin J, Duan J, Cui Z, Ren W, Li T, Yin Y. Hydrogen peroxide-induced oxidative stress activates NF-κB and Nrf2/Keap1 signals and triggers autophagy in piglets. RSC Adv 2015a;5(20):15479–86. https://doi.org/10.1039/c4ra13557a.
Yin J, Liu M, Ren W, Duan J, Yang G, Zhao Y, Fang R, Chen L, Li T, Yin Y. Effects of dietary supplementation with glutamate and aspartate on diquat-induced oxidative stress in piglets. PLoS One 2015b;10(4):e0122893. https://doi.org/10.1371/journal.pone.0122893.
Yin J, Wu M, Li Y, Ren W, Xiao H, Chen S, Li C, Tan B, Ni H, Xiong X, Zhang Y, Huang X, Fang R, Li T, Yin Y. Toxicity assessment of hydrogen peroxide on Toll-like receptor system, apoptosis, and mitochondrial respiration in piglets and IPEC-J2 cells. Oncotarget 2017;8(2):3124–31. https://doi.org/10.18632/oncotarget.13844.
Yin L, Li J, Wang H, Yi Z, Wang L, Zhang S, Li X, Wang Q, Li J, Yang H, Yin Y. Effects of vitamin B6 on the growth performance, intestinal morphology, and gene expression in weaned piglets that are fed a low-protein diet1. J Anim Sci 2020;98(2). https://doi.org/10.1093/jas/skaa022.
Yin Y, Liu Y, Duan G, Han M, Gong S, Yang Z, Duan Y, Guo Q, Chen Q, Li F. The effect of dietary leucine supplementation on antioxidant capacity and meat quality of finishing pigs under heat stress. Antioxidants (Basel) 2022;11(7). https://doi.org/10.3390/antiox11071373.
Yin YB, Guo SG, Wan D, Wu X, Yin YL. Enteroids: promising in vitro models for studies of intestinal physiology and nutrition in farm animals. J Agric Food Chem 2019;67(9):2421–8. https://doi.org/10.1021/acs.jafc.8b06908.
Yoon BK, Jackman JA, Valle-González ER, Cho NJ. Antibacterial free fatty acids and monoglycerides: biological activities, experimental testing, and therapeutic applications. Int J Mol Sci 2018;19(4). https://doi.org/10.3390/ijms19041114.
You L, Lee AV, Oh SY, Fisher-Heffernan RE, Edwards M, de Lange K, Karrow NA. Effect of lipopolysaccharide-induced immune stimulation and maternal fish oil and microalgae supplementation during late pregnancy on nursery pig hypothalamic-pituitary-adrenal function1. J Anim Sci 2019;97(7):2940–51. https://doi.org/10.1093/jas/skz166.
Yu C, Xiao JH. The keap1-Nrf2 system: a mediator between oxidative stress and aging. Oxid Med Cell Longev 2021;2021:6635460. https://doi.org/10.1155/2021/6635460.
Yu X, Fu C, Cui Z, Chen G, Xu Y, Yang C. Inulin and isomalto-oligosaccharide alleviate constipation and improve reproductive performance by modulating motility-related hormones, short-chain fatty acids, and feces microflora in pregnant sows. J Anim Sci 2021;99(10). https://doi.org/10.1093/jas/skab257.
Yun W, Song M, Lee J, Oh H, An J, Kim G, Lee S, Lee S, Kim HB, Cho J. Arginine addition in a diet for weaning pigs can improve the growth performance under heat stress. J Anim Sci Technol 2020;62(4):460–7. https://doi.org/10.5187/jast.2020.62.4.460.
Zhang J, Xu W, Yang Y, Zhang L, Wang T. Leucine alters blood parameters and regulates hepatic protein synthesis via mammalian/mechanistic target of rapamycin activation in intrauterine growth-restricted piglets. J Anim Sci 2022a;100(4). https://doi.org/10.1093/jas/skac109.
Zhang L, Liu C, Jiang Q, Yin Y. Butyrate in energy metabolism: there is still more to learn. Trends Endocrinol Metabol 2021;32(3):159–69. https://doi.org/10.1016/j.tem.2020.12.003.
Zhang N, Jing W, Cheng J, Cui W, Mu Y, Li K, Lei X. Molecular characterization and NF-κB-regulated transcription of selenoprotein S from the Bama mini-pig. Mol Biol Rep 2011;38(7):4281–6. https://doi.org/10.1007/s11033-010-0551-y.
Zhang S, Johnson JS, Trottier NL. Effect of dietary near ideal amino acid profile on heat production of lactating sows exposed to thermal neutral and heat stress conditions. J Anim Sci Biotechnol 2020a;11:75. https://doi.org/10.1186/s40104-020-00483-w.
Zhang S, Wu Z, Heng J, Song H, Tian M, Chen F, Guan W. Combined yeast culture and organic selenium supplementation during late gestation and lactation improve preweaning piglet performance by enhancing the antioxidant capacity and milk content in nutrient-restricted sows. Anim Nutr 2020b;6(2):160–7. https://doi.org/10.1016/j.aninu.2020.01.004.
Zhang S, Zhao J, Hu J, He H, Wei Y, Ji L, Ma X. Gama-aminobutyric acid (GABA) alleviates hepatic inflammation via GABA receptors/TLR4/NF-kappaB pathways in growing-finishing pigs generated by super-multiparous sows. Anim Nutr 2022b;9:280–90. https://doi.org/10.1016/j.aninu.2022.02.001.
Zhang T, Chi Y, Ren Y, Du C, Shi Y, Li Y. Resveratrol reduces oxidative stress and apoptosis in podocytes via Sir2-related enzymes, Sirtuins1 (SIRT1)/Peroxisome proliferator-activated receptor gamma Co-activator 1alpha (PGC-1alpha) Axis. Med Sci Mon Int Med J Exp Clin Res 2019a;25:1220–31. https://doi.org/10.12659/MSM.911714.
Zhang T, Zhou YF, Zou Y, Hu XM, Zheng LF, Wei HK, Giannenas I, Jin LZ, Peng J, Jiang SW. Effects of dietary oregano essential oil supplementation on the stress response, antioxidative capacity, and HSPs mRNA expression of transported pigs. Livest Sci 2015;180:143–9. https://doi.org/10.1016/j.livsci.2015.05.037.
Zhang W, Bao C, Wang J, Zang J, Cao Y. Administration of Saccharomyces boulardii mafic-1701 improves feed conversion ratio, promotes antioxidant capacity, alleviates intestinal inflammation and modulates gut microbiota in weaned piglets. J Anim Sci Biotechnol 2020c;11(1):112. https://doi.org/10.1186/s40104-020-00516-4.
Zhang X, Chen T, Lim J, Gu F, Fang F, Cheng L, Campanella OH, Hamaker BR. Acid gelation of soluble laccase-crosslinked corn bran arabinoxylan and possible gel formation mechanism. Food Hydrocolloids 2019b;92:1–9. https://doi.org/10.1016/j.foodhyd.2019.01.032.
Zhang Y, Lu T, Han L, Zhao L, Niu Y, Chen H. L-glutamine supplementation alleviates constipation during late gestation of mini sows by modifying the microbiota composition in feces. BioMed Res Int 2017;2017:4862861. https://doi.org/10.1155/2017/4862861.

Zhang Y, Wang Y, Chen D, Yu B, Zheng P, Mao X, Luo Y, Li Y, He J. Dietary chlorogenic acid supplementation affects gut morphology, antioxidant capacity and intestinal selected bacterial populations in weaned piglets. Food Funct 2018;9(9):4968–78. https://doi.org/10.1039/c8fo01126e.

Zhang Z, Zhang G, Zhang S, Zhao J. Fructooligosaccharide reduces weanling pig diarrhea in conjunction with improving intestinal antioxidase activity and tight junction protein expression. Nutrients 2022c;14(3). https://doi.org/10.3390/nu14030512.

Zhao P, Piao X, Zeng Z, Li P, Xu X, Wang H. Effect of Forsythia suspensa extract and chito-oligosaccharide alone or in combination on performance, intestinal barrier function, antioxidant capacity and immune characteristics of weaned piglets. Anim Sci J 2017;88(6):854–62. https://doi.org/10.1111/asj.12656.

Zheng P, Yu B, He J, Tian G, Luo Y, Mao X, Zhang K, Che L, Chen D. Protective effects of dietary arginine supplementation against oxidative stress in weaned piglets. Br J Nutr 2013;109(12):2253–60. https://doi.org/10.1017/S0007114512004321.

Zhou H, Sun J, Ge L, Liu Z, Chen H, Yu B, Chen D. Exogenous infusion of short-chain fatty acids can improve intestinal functions independently of the gut microbiota. J Anim Sci 2020a;98(12). https://doi.org/10.1093/jas/skaa371.

Zhou Y, Lan R, Xu Y, Zhou Y, Lin X, Miao J. Resveratrol alleviates oxidative stress caused by Streptococcus uberis infection via activating the Nrf2 signaling pathway. Int Immunopharm 2020b;89(Pt A):107076. https://doi.org/10.1016/j.intimp.2020.107076.

Zhou Y, Zhou L, Ruan Z, Mi S, Jiang M, Li X, Wu X, Deng Z, Yin Y. Chlorogenic acid ameliorates intestinal mitochondrial injury by increasing antioxidant effects and activity of respiratory complexes. Biosci Biotechnol Biochem 2016;80(5):962–71. https://doi.org/10.1080/09168451.2015.1127130.

Zivanovic S, Li J, Davidson PM, Kit K. Physical, mechanical, and antibacterial properties of chitosan/PEO blend films. Biomacromolecules 2007;8(5):1505–10. https://doi.org/10.1021/bm061140p.

Zou Y, Wei HK, Xiang QH, Wang J, Zhou YF, Peng J. Protective effect of quercetin on pig intestinal integrity after transport stress is associated with regulation oxidative status and inflammation. J Vet Med Sci 2016;78(9):1487–94. https://doi.org/10.1292/jvms.16-0090.

van den Brink, F. T., L. Buter, M. Odijk, W. Olthuis, U. Karst and A. van den Berg. Mass spectrometric detection of short-lived drug metabolites generated in an electrochemical microfluidic chip. Anal Chem 2015;**87**(3): 1527-1535. doi: 10.1021/ac503384e

Hurst J, Kuehn S, Jashari A, Tsai T, Bartz-Schmidt KU, Schnichels S, et al. A novel porcine ex vivo retina culture model for oxidative stress induced by H_2O_2. Altern Lab Anim 2017;45(1):11–25. https://doi.org/10.1177/026119291704500105.