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Review Article

A Review: Using Yeast Extract as Feed Additive in Pig Diets

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Abstract | Currently, there is interest in identifying alternative feed additives to replace antibiotic growth promoters in pig diets. This article reviewed the effects of using different types of yeast extract (YE), their fractions, and the dosage as feed additive on the growth performance, immune function, and gut morphology of pigs. Inconsistent results have been reported for the various yeast products utilized in the animal feed industry, with differing types of YE processing (autolysis or hydrolysis) and differing doses/responses. In a feed additive, the components of the cell wall (β-glucan and mannan-oligosaccharides) and some of their cellular metabolites are key beneficial factors in promoting the growth performance, immunological response, gut morphology, gut microbiota, and feed consumption of pigs.

Keywords | Yeast extract, Yeast cell wall, Performance, Immune, Pig

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INTRODUCTION

Currently, the use of antibiotics in animal feed is restricted due to concerns that residues in animal products may be harmful to human health. In the European Union, antibiotics have been banned as a growth promoter from animal feed since 2006. Furthermore, the government of Thailand has also banned antibiotics as a growth promoter in animal feed since 21 August 2015 (Gelband et al., 2015). Thus, there has been a focus on identifying suitable alternative feed additives to replace the use of antibiotic growth promoters (Kaya et al., 2015; Lee et al., 2015) and in particular, whole cell yeast cell or yeast cell wall produce from *Saccharomyces cerevisiae* (Shang et al., 2018).

Using different dietary yeast products improve productive performance, mucosal immunity, and intestinal development, as well as adsorbing mycotoxins and gut microbiota and reducing postweaning diarrhea in pigs have been reported (Shen et al., 2009; Jiang et al., 2015, Yang et al. 2016). The beneficial production responses in pigs have been attributed to enzymes, vitamins, and other nutrients or growth factors contained in the yeast products (Shen et al., 2009).

Mannan-oligosaccharides (MOS) and β- glucans are the large part of cell wall of yeast and are accountable for effectiveness of the yeasts (Shen et al., 2009). Nucleotides in the yeast also support rapid growth of tissue and organ systems in piglets, since the synthesis of these depends on the availability of the nucleotides (Waititu et al., 2017). Hu et al. (2014) reported that supplementation of yeast extracts rich in nucleotides positively transformed the gut microbial profile in piglets. Therefore, this article reviewed the effects of extracted yeast (whole and fragments of yeast) on the productive performance, immune response, and gut

health and the appropriate inclusion rate in pig diets.

Non-antibiotic feed additives in pig diets

Before 2006, antibiotics were commonly added in feed as growth promoters to reduce enteric infections (Budino et al., 2005), to improve the ecology of intestinal microorganism and to reduce post weaning diarrhea in piglets (Sorensen et al., 2009). However, the use of antibiotics promoted resistant gene of pathogenic bacteria (Budino et al., 2005) that contaminated the food chain (Chen et al., 2005). Management and nutritional strategies must be considered to avoid the adverse effects of eliminating antibiotics from diets (Kil and Stein, 2010; Liu et al., 2017). The adverse effects on productive performance of removing antibiotics from the diet are more pronounced during the starter period rather than during the growing-finishing period (Cardinal et al., 2021). Various alternative feed additives (probiotics, prebiotics, organic acids, phytogenic and yeast products), have been applied to replace the use of antibiotics (Vondruskova et al., 2010).

Yeast extract products

The yeast extract was initially produced from brewer's yeast cells (In et al., 2005). After fermentation process, the yeast cells were washed, centrifuged, heated, and dried (Håkenåsen, 2017). There are two yeast extraction production processes: autolysis, using the yeast's own enzymes or hydrolysis, using added exogenous enzymes (Anwar et al., 2017; Alves et al., 2021). Once the lysis process is complete, the yeast extract (the intracellular soluble fraction) and the cell walls are separated using centrifugation before being dried (Bzducha-Wróbel et al., 2014).

Although autolysis is cheaper than hydrolysis, smaller fractions of yeast are produced using hydrolysis (Mohd Azhar et al., 2017); consequently, they contain higher levels of yeast nucleotides in the extract (Anwar et al., 2017; Mohd Azhar et al., 2017). Avramia and Amariei (2021) reported that yeast produced using autolysis contains MOS on the outside, while hydrolyzed yeast contains a mixture of MOS and β-glucans on the outside. It seems that the hydrolysis of yeast cells by enzymatic method is more applicable due to a low salt concentration (Nagodawithana, 1992; Podpora et al., 2015). However, when the process of autolysis is accurately performed, free amino acids and peptides from the lysis yeast cell are also fit to nutritional requirement of animal (Podpora et al., 2015). On the other hand, yeast from the bioethanol process has already been inactivated during the downstream processing of the bioethanol (Mohd Azhar et al., 2017), with the addition of exogenous proteases resulting in lysis of the yeast and more hydrolysis of the mannoproteins outside the yeast (Mohd Azhar et al., 2017). Gao et al. (2021) reported that yeast extract contained 41.31% CP, 7.38% ash, and 10.37% total nucleic acid. However, inconsistencies in the composition of yeast extracts are summarized in Table 1.

Autolyzed Yeast (AY)

AY is produced from cell degradation by its own enzymes (Bortoluzzi et al., 2009) and is considered an irreversible process (Schiavone et al., 2014). The yeast from alcohol production (molasses fermentation) is used to produce AY (Berto et al., 2020). There are 2 autolysis processes: 1) induced autolysis; and 2) natural autolysis (Alexandre and Guilloux-Benatier, 2006). Nucleotides, amino acids and antioxidants from induced autolysis yeast cells are used for the food and cosmetic industries (Liu et al., 2017; Wang et al., 2018), while natural autolysis occurs during the process of fermentation and aging (electrical, enzymatic, physical, and chemical) (Alexandre and Guilloux-Benatier, 2006; Liu et al., 2017). In term of autolysis, the environmental pH and temperature of live yeasts are controlled and drying with a process of spray dry (Berto et al., 2020). Numerous enzymes such as protease, β (1-3), β (1-6) glucanase, mannase, and kitanase are released from yeast cell by autolysis process (Boonraeng et al., 2000; Torresi et al., 2014). Although productivity and efficiency of yeast extraction yield and the separation process of solid-liquid are low, it has several advantages, including no chemicals or enzymes are needed in the process, which saved the cost and reduce the steps of the process (Khan et at., 2020).

The composition of AY has been summarized as: 3.5–3.9% nucleic acids, 11–22% of β-glucan, 3–12% MOS, 30.0–41.1% crude protein, and 2.51–5.00 % crude fat (Berto et al., 2020; Namted et al., 2021). Using 0.2–0.5% AY as a feed additive in pig diets seemed to improve the performance and immune function of weaned and finished pigs (Upadhaya et al., 2019; Berto et al., 2020; Namted et al., 2021) (Table 2).

Hydrolysis Yeast (HY)

There are two steps (autolysis and enzymatic or acid hydrolysis) in hydrolyzing yeast cells to extract their cell content. Several investigators indicated that enzymatic hydrolysis was an useful process to enhance the quality of HY (Nagodawithana,1992; Jiang et al., 2010; Podpora et al., 2015). However, the manufacturers do not prefer the process of hydrolysis by acid due to the high salt and carcinogen contents in the products (Podpora et al., 2016). The mixture of enzymes includes protease, cellulase, hemicellulase, pectinase, glucanase and mannase are present in yeast cell (Andrews and Asenjo, 1987; Łubek-Nguyen et al., 2022).

The chemical components of HY include: 3.5% nucleic acids, 22.43–23% β-glucan, 15–15.6% MOS, 40.0–53.2% crude protein, and 1.8–2.3% crude fat (Hu et al., 2014;

Table 1: Differing reports of yeast extract components

β-Glucans (%)	Mannan-oligosaccharides (%)	Chitin (%)	Nucleotides, amino acids and peptides (%)	Lipid (%)	References
50–60	35–40	2	nd	nd	Eicher et al. (2006) Anwar et al. (2017)
29–64	31	nd	13	9	Jaehrig et al., 2008)
11-22	3-12	nd	3.5-3.9	2.51-5.00	Berto et al. (2020) Namted et al. (2021)
22.43-23.00	15-15.6	nd	3.5	1.8-2.3	Hu et al. (2014) Zhang et al. (2019) Boontiam et al. (2022) Sampath et al. (2021)

Table 2: Dosage summary of autolyzed yeast in pig diets

Study	Pig type	Level	Performance	Digestibility	Immune	gut microbiota	Meat quality
Upadhaya et al. (2019)	weaned	0.2	0	0	0	+	nd
Upadhaya et al. (2019)	weaned	0.4	+	0	0	+	nd
Berto et al. (2020)	weaned	0.4-0.5	+	nd	+	0	nd
Namted et al. (2021)	finisher	0.5	+	nd	+	nd	+

+ = Improve, 0 = No effect, nd= No data

Table 3: Dosage summary of hydrolysis yeast in pig diets

Study	Pig type	Level	Performance	Villi	Digestibility	Immune	Gut microbiota	Meat quality
Price et al. (2010)	Weaned	0.2	+	+	nd	nd	+	nd
Šperanda et al. (2013)	Weaned	0.2	0	nd	nd	+	nd	nd
Jensen et al. (2013)	Weaned	0.2	0	nd	nd	nd	+	nd
Molist et al. (2014)	Weaned	0.2	+	nd	nd	+	0	nd
Hasan et al. (2018)	Sow	0.2	+	nd	nd	0	+	nd
Keimer et al. (2018)	Weaned	1	+	+	+	nd	nd	nd
Zhang et al. (2019)	Grower	0.05-1	+	nd	+	0	nd	0
Sampath et al. (2021)	Finisher	0.1	+	nd	+	nd	+	+

+ = Improve, 0 = No effect, nd=No data

Table 4: Yeast cell wall composition

Item	Cell wall mass (%, dry weight)	Molecular structure
β-Glucans	50–60	Branched beta-1,3- and beta-1,6-glucans
Mannan-oligosaccharides	35–40	Long chains of alpha-1,6-linked mannoses with short branches of alpha-1,2 and alpha-1,3 mannoses
Chitin	1–2	Long linear homopolymer of beta-1,4-linked N-acetylglucosamine

Sources: Bowman and Free, 2006; Shaun et al., 2006; Ponton, 2008; Anwar et al., 2017; Garcia-Rubio et al., 2020; Lee et al., 2021

Table 5: Summary of studies evaluating effects of supplementing pig diets with β-glucans from yeast cell wall

Dosage (% of diet)	Response	Reference
0.025	- Increased average daily gain and average daily feed intake	Dritz et al. (1995)
0.1	- No effect on digestibility of dry matter, nitrogen or grossenergy	Ko et al. (2000)
0.015, 0.03	- Increased feed intake - No effect on immunity	Hiss and Sauerwein (2003)

0.0005	- No effect on growth hormone - Benefits on somatotropic axis and immune function	Li et al. (2006)
0.02	-Increased digestibility of dry matter and gross energy	Hahn et al. (2006)
0.01	- Increased immune functions	Wang et al. (2008)
0.05, 0.075	- Reduced fecal excretion of F4+ *Escherichia coli* (enterotoxigenic *E coli*)	Stuyven et al. (2009)
0.0025	- Reduced Enterobacteriaceae counts and pro-inflammatory - No influence on performance	Sweeney et al. (2012)
0.01	- Not effect on performance	Zhou et al. (2013)
0.02	- Decreased fecal *E coli* - Improved immune function (challenged with lipopolysaccharide)	Zhou et al. (2013)
0.0015	- Improved growth - Improved phagocytic activity and Interleukin-2 production - Decreased cortisol and tumor necrosis factor alpha levels	Vetvicka and Oliverira (2014)
0.1	- Decreased synthesis of inflammatory mediators	Saleh et al. (2015)

Zhang et al., 2019; Sampath et al., 2021; Boontiam et al., 2022). The effective inclusion rates of HY in diets for the weaned, grower, and finisher periods are 0.1–0.2%, 0.05–1.0%, and 0.1%, respectively (Table 3). Therefore, compared to AY supplementation, it seems that the inclusion level of HY is lower.

Mode of action in yeast cell wall

Yeast extracts contain protein, nucleotides and polysaccharides (β-glucan and α-mannan). These compounds are believed to promote the growth performance, immune function, and gut function of piglets (Gallois et al., 2009; Lee et al., 2021). The yeast extract contains cell wall polysaccharides (21.6 %), crude protein (32.7-43.8%), carbohydrates (14.3 %), and nucleotides (1.1-6.0 %) (Pereira et al., 2016; Waititu et al., 2016). The components in the yeast cell wall are summarized in Table 4. Furthermore, the extracted products from the inner cell wall of yeast can be define as functional nutrients since there are high containing of peptides, inositol (growth promotion), glutamic acid (improve palatability), and nucleotides (cell growth) (Pereira et al., 2012).

Yeast cell walls contain three main polysaccharides: β-glucans, mannan-oligosaccharides (MOS), and chitin. The strain of yeast (for breweries or bioethanol) significantly influences the final composition of the cell wall (Hajar et al., 2017). Mohd Azhar et al. (2017) reported that carbon sources (sugar or starch), temperature, pH, and oxygen availability affect the presence of sugars in the walls, the structure of polymers, and the degree and length of branching. Finally, the production process (autolysis or hydrolysis) applied to the cell walls also influences the composition of the cell wall (Bzducha-Wróbel et al., 2014).

β-Glucans

Vetvicka and Vetvickova (2014) reported that β-Glucans are complex glucose polymers that found in the cell wall of yeast, fungi, algae, and some cereal grains. The source and the type of chemical bond in the polymers of glucose cause difference structure of β-glucans (Synytsya and Novak, 2014). Side-chain-linked glucose at the 1 and 6 C atoms are seen in Fungal and yeast β-glucans (Schwartz and Vetvicka, 2021), while the unbranched β-glucans with glucopyranose molecules linked by 1,3-β and 1,4-β linkages are found in the cell wall of cereal grains (Laroche and Michaud, 2007).

About 50–60% of polysaccharides of total yeast cell wall are β-Glucans that can stimulate biological functions of animal (Eicher et al., 2006) due to the β-1,3/1,6 glycosidic linkages of glucan from the cell wall increasing the macrophages and neutrophils function, lowering immunosuppression, and decreasing adverse effects of gram-negative bacteria after weaning (Eicher et al., 2006).

Li et al. (2006) showed that supplementing β-glucans from yeast partly reduce proinflammatory cytokines TNF- and IL-6 synthesis, while up-regulating anti-inflammatory cytokine IL-10 that inhibits T cell proliferation in weaned pigs. β-Glucans as a feed additive for early weaned piglets showed protective effects against enterotoxigenic *E coli* infection by reducing bacterial excretion and diarrhea (Stuyven et al., 2009). Sweeney et al. (2012) showed that β-glucans reduced the Th 17 signature cytokine IL-17a expression in the colon of weaned pigs. Ryan et al. (2012) reported that supplementing β-glucans reduced the Th 17 signature molecule IL-17a and reduced the Th 17-related cytokines (IL-17a, IL-17F, and IL-22), receptor IL23R, and IL-6 expression in the colon of piglets (aged 49 days). The dosage of β-glucans supplementation and the responses of pigs in various studies are presented in Table 5.

Improvements in productive performance or immune functions have been reported after adding 0.0005–0.1% β-glucans from the yeast cell wall to pig diets (Table 5), though the effect of the additions was inconsistent. Vetvicka

and Vetvickova (2020) suggested this inconsistency was due to the dose-dependent manner. Additionally, this may be caused by the solubility of β-glucan since Vetvicka and Oliverira (2014) reported that β-glucan from *S. cerevisiae* was 68.5% insoluble, while Sweeney et al. (2012) reported that 90% water insoluble β-glucans are derived from the yeast. Compared to inclusion rates for AY (0.2–0.5% of diet) or HY (0.05–1.0% of diet), supplementing with β-glucan has been at much lower levels than those for yeast extracts.

Mannan-oligosaccharides (MOS)

MOS is a glucomannoprotein complex (in the form of mannosylated proteins) isolated from the outer cell wall of the yeast (*S. cerevisiae*) (Davis et al., 2002; Avramia and Amariei, 2021). The mannan is extracted from soluble cell wall of yeast (Li and Karboune, 2018). Brady et al. (1994) and White et al. (2002) reported that whole cell yeast contains approximately 5.2-7.75% MOS.

Mannan contains a high volume of mannan reactive units (α– 1,3 mannan) associated with the phagocytic cell's agglutination and the recognition (Brümmer et al., 2010). The ability has been reported that mannans attach mannose-binding proteins of bacteria surface, then protect the colonization of bacteria in the intestinal tract (Spring et al., 2000; Davis et al., 2004b). MOS are capable of adsorbing entero-pathogens (Spring et al., 2000; Kocher et al., 2004) and of increasing the population of beneficial bacteria in the gastrointestinal tract (Kogan and Kocher, 2007), with a consequent improvement in nutrient utilization. Shanmugasundaram and Selvaraj (2012) reported that MOS increased the T-cell and IL-10 mRNA contents and decrease the IL-1 mRNA content in the cecal tonsil, resulting in enhanced net anti-inflammatory production. Supplementation of MOS in the range 0.05–0.4% from the yeast cell wall was used as feed additive in pig diets (Table 6). However, it should be noted that using MOS may promote growth of pigs kept in a poor management conditions and poor productive performance (Halas and Nochta, 2012).

Chitin

Chitin is a linear (1 ,4)-linked 2-acetamido-2-deoxy-β-d-glucopyranan (N-acetyl-β-d-glucosaminane); chitosan is the deacetylated derivative of chitin (Lenardon et al., 2010). Chitosan is a bioactive polymer (a copolymer of N-acetyl-D-glucosamine and D-glucosamine) (Udayangani et al., 2017). Chitin is a minor component of the yeast cell wall (1–2% of dry wall) (Lesage and Bussey, 2006), while the major source of animal feed chitin is derived from insects (composed of 13–42% of chitin) (Xu et al., 2019). Adding chitin in feed promoted the antioxidation defense system via the scavenging capacity for free radicals (Xu et al., 2018). Xu et al. (2014) reported that levels of chitosan (0.01–0.2%, derived from the deacetylation of chitin) improved the average daily gain of weaned pigs. Chitosan (0.01% from the deacetylation of chitin) enhanced the productive performance, capacity of antioxidation, immune function, and intestinal function of weaned pigs (Wan et al., 2017). However, there is few information available on dosage recommendations for chitin from yeast cell walls.

Cellular contents of yeast extract

Nucleotides in yeast (NY): Yeast can be a source of nucleotides that are structure of DNA and RNA, a phosphate group (adenine, cytosine, guanine, or thymine bases) and a pentose sugar (Tibbets, 2002; Bacha et al., 2013). Yeasts are a source of nucleobases, nucleosides, and nucleotides; especially, adenosine (1,497 mg kg^{-1}) and guanosine (1,445 mg kg^{-1}) (Pastor-Belda et al., 2021). Nucleotides are significantly required by cell replication process, particularly intestinal epithelial and lymphoid cells, which have low capacity of nucleotides synthesis (Waititu et al., 2017).

Approximately, 12– 20% of total nitrogen in yeast are derived from nucleic acids (purine and pyrimidine bases of nucleoproteins) (Rumsey et al., 1992). NY may improve nutrient digestibility, due to the development of jejunal morphology of pig (Shen et al., 2009). Furthermore, NY also promotes epithelium cell function in the intestinal tract by increasing the synthesis of mucosal protein, and increasing the ratio of the maltase/lactase enzyme (Uauy et al., 1990; Pérez et al., 2004). Rumsey et al. (1992) found that using RNA extract from yeast increased hepatic nucleic acids, and providing nucleic acids in diet could be utilized by the tissue.

Supplementing nucleotides in diet stimulate immune system of the animal (Grimble and Westwood, 2001). Although the mechanism of nucleotides on the stimulation of gut immune system is unclear, being building blocks of ATP, DNA, and RNA is emphasis (Grimble and Westwood, 2001). The nucleotides from yeast extract also involve with the functions of interleukin (IL)-1β, IL-6, IL-10, TNF-α, and the programmed cell death gene-1 (PD-1) (Waititu et al., 2017). The effects of supplementing NY in pig diets are summarized in Table 7.

Other compounds: There are other cellular chemical components in yeast cells, such as amino acids, peptides, proteins, lipids, long chain fatty acids, diacetyl, α-acetolactic acid, ethyl decanoate, oxidized polyphenols, oxidized α-acid, and alkaline substance (Wang et al., 2018). High concentration of umami-taste amino acids, peptides, and nucleotides in yeast improve the palatability and feed intake of the animal (Foster, 2011; Keimer et al., 2018). Jung et al. (2011) and Jung et al. (2016) reported that

Table 6: Summarized effects of dietary mannan-oligosaccharides from yeast cell walls on growth performance and immune response

Dosage (% of diet)	Response	Reference
0.2	- Improved gain and efficiency - Improved feed intake - No effect on lymphocyte proliferation	Davis et al. (2002)
0.1	- Improved feed intake	Davis et al. (2002)
0.05	- Improved feed intake - Improved average daily gain	Davis et al. (2002)
0.05, 0.1	- Improved growth performance - Improved nutrient digestibility	LeMieux et al. (2003)
0.20	- Increase average daily gain	LeMieux et al. (2003)
0.3	- Reduce ratio of cluster of differentiation (CD) $CD3^+CD4^+$: $CD3^+CD8^+$ T lymphocytes from jejunal lamina propria tissue - Improved gain and efficiency	Davis et al. (2004a)
0.2, 0.3	- Improved gain: feed - No effect on lymphocyte proliferation	Davis et al. (2004b)
0.2, 0.3	- Increased average daily feed intake and average daily gain	Rozeboom et al. (2005)
0.4	- Improved body weight gain	Tassinari et al. (2007)
0.1	- Enhanced specific and non-specific immune responses	Nochta et al. (2010)
0.10	- Improved growth performance - Improved dry matter digestibility	Zhao et al. (2015)
0.1, 0.2	- Improved growth performance - Improved bacterial population balance - Reduced incidence of diarrhea	Tuoi et al. (2016)
0.08	- Increased serum concentrations of Immunoglobulin (IgG and IgA), complement (C3) and lysozyme - Improved body weight gain	Duan et al. (2016)
0.2	- Enhanced immune responses and - Reduced gut microbiota - No effect on growth	Valpotić et al. (2018)
0.08	- Increased acetic acid concentrations - Improved microbial richness and diversity - Improved intestinal health - Improved growth performance - Improved nutrient digestibility	Zhang et al. (2021)
0.05	- Improved growth, - Improved fecal dry matter, or antimicrobial resistance of fecal *E. coli*	Chance et al. (2021)

Table 7: Summary of dosage effects of nucleotides yeast in pig diets

Study	Pig stage	Level	Performance	Villi	Digestibility	Immune	Gut microbiota
Moore et al. (2011)	Weaned	0.2	+	nd	nd	=	nd
Superchi et al. (2011)	Weaned	0.1	+	nd	nd	+	nd
Sauer et al. (2011)	Weaned	0.1	nd	=	=	nd	=
Waitutu et al. (2019)	Weaned	0.1	=	+	nd	+	+
Patterson et al. (2019)	Weaned	0.1, 0.2	+	nd	nd	nd	+
Gao et al. (2021)	Sow	0.4	+	+	nd	+	nd
Chance et al. (2021)	Weaned	0.05	=	nd	=	nd	=

+ = Improve, 0 = No effect, nd=No data

Cyclo-His-Pro (CHP) contained in yeast associate with mechanism of leptin. This compound is generally found in body fluids and gastrointestinal tract (Jung et al., 2016). Minelli et al. (2008) reported that the CHP may be in-

volved with the mechanisms of presynaptic dopaminergic and a leptin-like function in the central nervous system. Thus, CHP clearly suppress feed intake, consequent reduce the glycemic index and body weight in obese animals (Jung et al., 2011).

CONCLUSIONS

Using YE as a feed additive has beneficial effects on pig production via the improvement of immune function, gut morphology, anti-inflammation and increased gut microbiota (Figure 1). However, the physiological responses of pigs differ depending on the type, dosage of YE (AY, HY, or their components), and the conditions of the pigs. The appropriate inclusion of HY in diets is at a lower rate than for AY. It seems that β-glucan and mannan-oligosaccharides from the cell wall are the main factors influencing the immune response, while nucleotides promote pig gut morphology. Finally, other chemical compounds, such as a peptide or CHP, may be involved with the mechanism of feed intake.

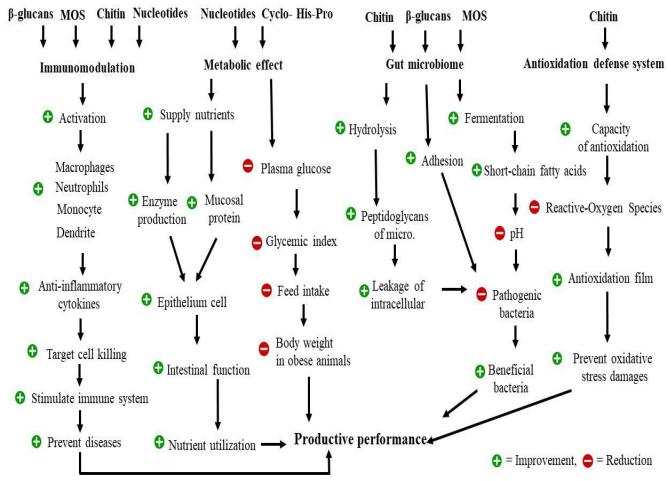

Figure 1: Summary of diagram about the mechanism of the yeast cell wall and cellular content on improving immune function, gut morphology, and microbiota in pig.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

AUTHORS CONTRIBUTION

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