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The effect of anti-microbial peptide on the performance, survival rate, and diarrhea ratio the pig: A meta-analysis

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ABSTRAK

Penelitian ini bertujuan untuk mengetahui pengaruh pemberian anti-mikrobial peptida pada pertumbuhan babi menggunakan meta-analisis. Bangun data disusun dari berbagai publikasi yang merujuk pada penggunaan anti-mikrobial peptida pada pertumbuhan babi. Metode yang digunakan dalam penelitian dalam menyeleksi artikel yang dipublikasi menggunakan metode Sistematika Review untuk Percobaan pada Hewan (SYRCLE's). Bangun data akhir terdiri dari 41 studi *in-vivo*. Data dianalisa menggunakan perangkat lunak R Studio versi 3.6.30. Hasil meta-analisis menunjukan bahwa penggunaan AMP memberikan pengaruh nyata (p < 0,05) pada total keseluruhan bobot badan, konsumsi pakan harian, dan pertumbuhan bobot badan harian pada fase pemeliharaan babi. Hasil meta-analisis juga menunjukan bahwa penggunaan AMP dapat menurunkan nilai konversi pakan, tingkat kematian, dan gejala diare pada babi (p < 0,05). Hasil meta-analisis menunjukan tingkat optimal pada penggunaan AMP yaitu 21,40 mg/kg dan nilai konversi pakan 1,47 tergantung dari bentuk yang diberikan. Kesimpulan dari penelitian ini adalah baik bentuk dan dosis pemberian anti-mikroba memberikan efek menguntungkan pada kinerja pertumbuhan babi.

Kata Kunci : Anti-mikrobial Peptide, Kinerja-pertumbuhan, Meta-analisis, Babi

ABSTRACT

A meta-analysis conducted to determine effect of anti-microbial peptide (AMP) form on the performance of pig. A database was designed based on data published that reported used probiotic on pig. The method used in the selection of articles was based on the systematic review center for laboratory animal experimentation (SYRCLE's) method. The final database consisted of 41 in vivo studies with 241 treatments. The analysis statement in the system were R Version 3.6.30. In general, in the total phase, body weight and survival rate increased ($p <0.05$; quadratic) due to AMP administration. In continued of the phase 1, growth performance parameters [eg, body weight, average daily gain (ADG), and average daily intake (ADI), feed conversion ratio (FCR)] increased ($p <0.05$; quadratic) and FCR decreased ($p <0.05$; quadratic) due to SAP administration. In the total phase, parameters such as body weight, ADG, and survival rate increased ($p <0.05$; quadratic) while ADI tended to increase ($p <0.1$; linear) due to the increase in the CAP dose. Meanwhile, other parameters in the total phase, i.e. FCR decreased ($p <0.05$; quadratic). The optimal dose of CAP for the total phase was 21.406 mg/kg of feed with a predicted minimum FCR of 1.47. The AMP forms (SAP and CAP) improved ($p <0.05$) the parameters of body weight, ADG, ADI, FCR, diarrhea ratios, and survival rate at each phase. In summary, both form and dosage of the anti-microbial help to beneficial effect on the growth performance of pigs.

Keywords: Anti-microbial peptide, Growth Performance, Meta-analysis, Pigs

INTRODUCTION

Antibiotic growth promoters (AGPs) has been used worldwide for more than 40 years. Dependence on the use of antibiotics in feed must consider several aspects including: the relatively expensive cost, the presence of harmful residues that are left because the antibiotics are absorbed in the digestive tract and accumulated in the blood and can create resistant microorganisms in livestock, especially pathogenic microbes such as *Salmonella. sp*. and *Escherichia coli* (Maron *et al.,* 2013).With the development of industry 4.0, including animal husbandry and animal health, some technologies lead to efficient use of production inputs in livestock businesses that can be applied as a substitute solution for artificial antibiotics, particularly the technology of the utilization of antimicrobial peptides. This technology has been implemented since the European Union (EU) banned antibiotics as feed additives. The ban on antibiotics as a feed additive began in 1997 when Avoparcin was officially banned from its use as an additive to animal feed by the European Union in Denmark (Maron *et al.,* 2013). The prohibition of antibiotics as an additive to animal feed extends to various countries, both in developed and developing countries, including Indonesia. Through the Animal Husbandry and Animal Health Law, Number 18 of 2009 Article 22 Paragraph 4c and Regulation of MOA Number 14/2017, the latest regulations regarding the prohibition of the use of AGPs in animal feed were applied as of January 1, 2018 (Sjofjan and Adli, 2021). This prohibition's impact has made many researchers, business actors, industry players, and breeders searching for alternatives to replace antibiotics, one of which is the antimicrobial peptide (AMP).

Antimicrobial peptides are molecules produced by cells in the tissues of living things that act as the body's defense system. The antimicrobial peptide can neutralize endotoxin produced by gram-negative bacteria. Based on the form of administration in pigs, AMP can be classified into a single antimicrobial peptide (SAP) and composite antimicrobial peptide (CAP). SAP is a peptide administered to pigs in a single form with high purity (more than 90%), such as lactoferrin (Wang *et al.,* 2006). CAP is a peptide in the form of a mixture or a peptide contained in crude extracts of functional proteins, for example, such as protamine-1 in potato protein, crude pig β-defensin 2 extracted from intestinal pig, and a mixture of pig defensin and fly antimicrobial peptide (Kim *et al.,* 2001; Jin *et al.,* 2008b; Ren *et al.,* 2015; Peng *et al.,* 2016). Defensins are classified into three types, i.e. alpha, beta, and theta defensins. The SAP dosage ranges from 0 to 1000 (mg/Kg of feed) while CAP ranges between 0 and 75000 (mg /Kg of feed). The maintenance period ranges from 1-14 days (phase 1), 15-28 days (phase 2), and 1-28 days (total). The general average for age and initial body weight is 22 days and 6.34 kg. Antimicrobial peptides administration both in the form of CAP and SAP still result in mixed effects. Research conducted by Yoon *et al.* (2012) and Yoon *et al.* (2013) show that administration in the form of SAP to piglets was able to improve production performance, intestinal health, improve digestibility, and reduce gram-negative bacteria. Furthermore, it was reported in the studies of Xiao *et al.* (2013) and Xiao *et al.* (2015) that the use of CAP in piglets was able to increase feed conversion, increase the immune system, and reduce organ damage. However, the use of CAP has not been able to improve daily body weight growth, and the average daily feed conversion (Xiao *et al.,* 2013). One method of answering this inconsistent resulted is to utilize statistical meta-analysis techniques. Therefore, this study aims to summarize and determine the effect of administering antimicrobial peptides on growth performance in pigs through meta-analysis studies from various sources of scientific publications.

MATERIAL AND METHODS

The selected journals were taken from PubMed, Google Scholar, Science Direct, and Open Science databases using keywords: probiotic, laying hens, performance, organ weight, carcass, and serum blood. The raw database information from articles, authors, year of study, diet used in trial, length of trial, level of treatment, form and dosage of probiotic contained in the study was recorded in a spreadsheet following Yoon *et al.* (2014) method. The parameters were growth performance (body weight, average daily gain, average feed intake, and feed conversion ratio); diarrhea ratio, and survival rate.

Criteria for articles to be included in database were as follows: (a) article were published in a peer-reviewed journals with range 2004-2019, (b) the pig were modern-controlled-trial environment and management, (c) non-antimicrobial peptide treatment excluded from the database, (e) the articles written consistent in English were considered in studies, (d) The parameters included in this studies were body weight, average daily gain, average daily intake, feed conversion ratio, diarrhea ratio, and survival rate at phase 1, phase 2, and total phase of growth. The database were converted into same unit. Likewise, data extraction was completed in accordance with the task analysis to obtain the exact values from graphical data, the relevant figure from the papers were subjection to an online tools of WebplotDigitizermethod. The final database were consisted of 41 in vivo studies . The details for the study selection included in meta-analysis are provided in Figure 1. While, the summary of the used of the final database is presented in Table 1.

Analyses of data

The phase was analyzed statistically using a mixed-model (Peng *et al.,* 2016; Yoon *et al.,* 2014; Yoon *et al.,* 2013). The analysis statement in the system used R Version 3.6.30 with the library “nlme” (Pinheiro *et al.,* 2020; R Core Team, 2020). The development of the studies were taken as the random effects, while the concentrations of supplementation were taken as the fixed effect. The mathematical formula used were following (Jin *et al.,* 2009; Ren *et al.,* 2015):

$$Y_{ijk} = \mu + s_i + \tau_j + s\tau_{ij} + B_1 X_{ij} + B_2 X_{ij}^2 + b_i X_{ij} + B_j X_{ij} + e_{ijk}$$

Where: Y_{ijk} = dependent variable, μ = averages all studies, s_i = randomized effect of experiment-$_i$, τ_j = fixed effect on the factor-j and factor τ, $s\tau_{ij}$ = randomized interaction between i experiment and j experiment from factor of τ, where Yij = dependent variable; B0 = overall intercept across all studies (fixed effect); B1 = linear regression coefficient of Y on X (fixed effect); B2 = quadratic regression coefficient of Y on X (fixed effect); Xij = value of the continuous predictor variable (AMP levels); si = value of random effect of study i; bi = random effect of study on the regression coefficient of Y on X in study i; and eij = the unexplained residual error.

RESULTS AND DISCUSSION

Based on the results of the meta-analysis, administering AMP increased (p <0.05; quadratic) body weight, averagre daily gain (ADG), and average daily intake (ADI), and decreased (p <0.05; quadratic) feed conversion ratio (FCR) in pigs in phase 1 (Table 2). In phase 2, the administration of AMP increased (p <0.05, squared) body weight, but decreased (p <0.05; linear) ADG and ADI. In general, in the total phase, body weight and survival rate increased (p <0.05; quadratic) due to AMP administration.

In phase 1, growth performance parameters (eg, body weight, ADG, and ADI) increased (p <0.05; quadratic) and FCR decreased (p <0.05; quadratic) due to SAP administration (Table 3). In phase 2, increasing the dose of SAP increased (p <0.05; quadratic) body weight and ADG while the FCR decreased (p <0.05; quadratic). In the total phase, body weight increased (p <0.05) following a quadratic pattern as the SAP dose increased. Some growth performance parameters from phase 2 (e.g., FCR) and of the total phase (e.g., ADG, ADI, and FCR) were not significantly different with the increasing of SAP dose. Based on the FCR, the optimal doses of SAP were 213 and 221 mg/kg of feed, for phase 1 and phase 2, respectively. The FCR values achieved at these optimal doses were 1.39 and 1.54, for phase 1 and phase 2, respectively. The increasing dose of CAP increased (p <0.05; quadratic) growth performance (e.g., body weight, ADG, and ADI) while FCR decreased (p <0.05; linear) in phase 1 (Table 4). In phase 2, bodyweight increased (p <0.05; quadratic) while ADG and ADI decreased (p <0.05; linear). In the total phase, parameters such as body weight, ADG, and survival rate increased (p <0.05; quadratic) while ADI tended to increase (p <0.1; linear) due to the increase in the CAP dose. Meanwhile, other parameters in the total phase, i.e. FCR decreased (p <0.05; quadratic). The optimal dose of CAP for the total phase was 21.406 mg/kg of feed with a predicted minimum FCR of 1.47.

The AMP forms (SAP and CAP) improved (p <0.05) the parameters of body weight, ADG, ADI, FCR, diarrhea ratios, and survival rate at each phase (Table 5). Meanwhile, the ADI parameter was significant (p <0.05) in phase 1 and the total phase, while in phase 2, it tended to be significant (p <0.1). In phase 2, the body weight and ADG parameters of SAP were higher (p <0.05) than those of CAP. Likewise, in the total phase, the ADG of SAP was higher (p <0.05) than those of the CAP.

The Effect of the AMP on Body Weight of pigs

The use of antimicrobial peptides (AMP) significantly improved body weight in pigs at each growth phase; this is consistent with the research of Berding *et al.* (2016); Boudry *et al.* (2007) and Cutler *et al.* (2007) in all maintenance phases as the increasing dose of SAP used in pigs increased body weight. The use of SAP in pigs helps increase the population of lactic acid bacteria in the digestive organs. Thus, intestinal health is maintained, and cell multiplication in

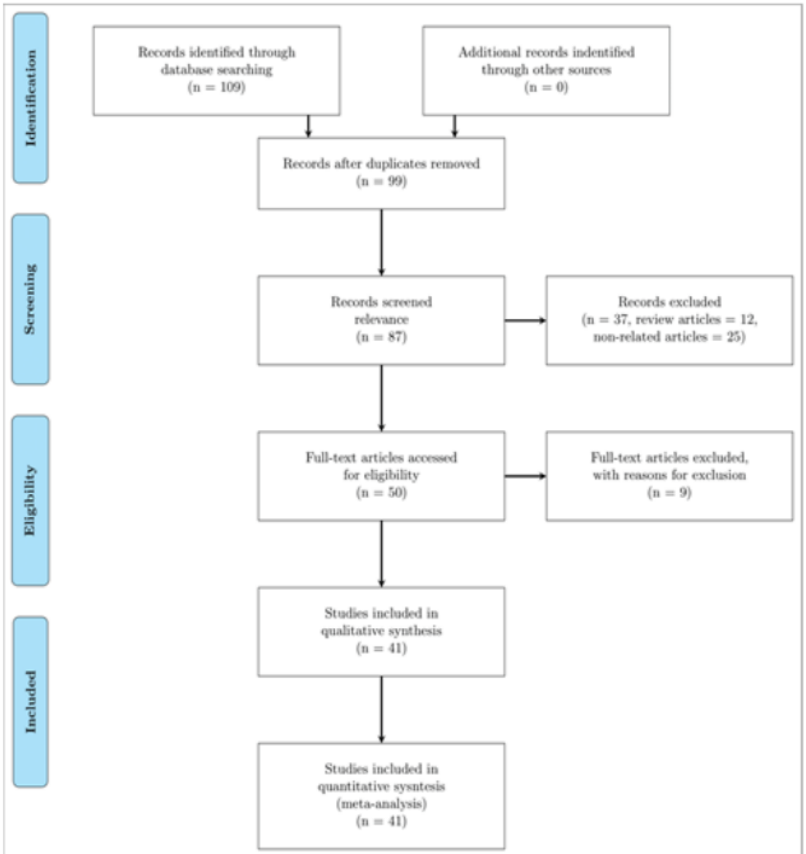

Figure 1. The Diagram of Selection of Articles According to Prisma-P (Shamseer et al., 2015)

the intestine increases. Increasing intestinal health can accommodate the absorption of the incoming nutrients, thereby increasing body weight in pigs. The use of SAP starts to stabilize when entering the third week of administration with increasing levels of administration (Boudry *et al.,* 2007). AMP from animals has consistently had a positive effect on the increasing growth of pigs (Berding *et al.,* 2006; Boudry *et al.,* 2007; Cutler *et al.,* 2007). Positive results are also reported in the research of Long *et al*. (2016) and May *et al*. (2012) that the use of AMP in the form of stable lysozyme (SAP) increases body weight gain, however, it has not been able to improve FCR in pigs significantly. The optimal dose of SAP was 120-200 mg/kg of total feed (Long *et al.,* 2016; May *et al.,* 2012).

The Effect of AMP on the ADG of Pigs

The use of AMP in the form of SAP can provide significant results on the average daily body weight growth in pigs. Research conducted by Tang *et al.* (2009; 2012; 2016) using SAP gave positive results on the average daily growth rate of pigs in phases 1 and 2. AMP that enters epithelial cells in the intestine works by fusion with other peptides and binds to the pepsin enzyme in pig blood. AMP that enters the blood is responsible for enhancing immune function and increasing the intestinal mucosal wall, when pigs entering the rearing age of 21 days (Tang *et al*.,

Table 1. Studies Included in the Meta-analysis of the effect of Anti-microbial Peptide on the Growth Performance in Pigs

No.	Reference	Antimicrobial peptide	Form	Dosage	Initial age[1)]	Rearing period			IBW
						Phase 1[2)]	Phase 2[2)]	Total[2)]	
1.	Berding *et al.*, 2016	Bovine lactoferrin	SAP	0 – 300	2	1 – 15	16 – 30	1 – 30	1.51
2.	Boudry *et al.*, 2007	Bovine colostrum	CAP	0 – 676	21	1 – 15	16 – 21	1 – 21	7.4
3.	Boudry *et al.*, 2008	Bovine lactoferrin	SAP	0 – 320	40	1 – 14	15 – 28	1 – 28	8.33
4.	Cutler *et al.*, 2007	Colicin E1	SAP	0 – 16.5	23	–	–	–	–
5.	DeRouchey *et al.*, 2004	Serume immunoglobulin G	CAP	0 – 11,450	17	1 – 14	15 – 24	1 – 24	6.09
6.	Huguet *et al.*, 2006	Bovine colostrum	CAP	0 – 50,000	21	–	–	1 – 35	6.3
7.	Huguet *et al.*, 2012	Bovine colostrum	CAP	0 – 40,000	28	1 – 6	–	–	7.8
8.	Jin *et al.*, 2008b	Potato protein	CAP	0 – 7,500	23	1 – 14	15 – 28	1 – 28	6.42
9.	Jin *et al.*, 2008a	Potato protein	CAP	0 – 7,500	23	1 – 14	15 – 28	1 – 28	7.2
10.	Jin *et al.*, 2009	Refined potato protein	CAP	0 – 600	23	1 – 14	15 – 28	1 – 28	5.96
11.	King *et al.*, 2008b	Bovine colostrum	CAP	0 – 75,000	21	1 – 7	–	–	6.65
12.	King *et al.*, 2008a	Bovine colostrum	CAP	0 – 50,000	14	1 – 14	–	–	3.6
13.	Lee *et al.*, 2010	Pig lactoferrin	SAP	0 – 50	21	–	–	1 – 28	5.9
14.	Long *et al.*, 2016	Lysozyme	SAP	0 – 120	25	1 – 14	15 – 28	1 – 28	7.76
15.	May *et al.*, 2012	Lysozyme	SAP	0 – 100	10	1 – 14	–	–	4.12
16.	Oliver and Wells, 2013	Lysozyme	SAP	0 – 100	24	1 – 14	15 – 28	1 – 28	7.85
17.	Oliver *et al.*, 2014	Lysozyme	SAP	0 – 100	26	1 – 14	15 – 28	1 – 28	8.65
18.	Peng *et al.*, 2016	Crude pig β-defensin 2	CAP	0 – 15,000	21	1 – 14	15 – 28	1 – 28	9.39
19.	Pierce *et al.*, 2005	Serume immunoglobulin G	CAP	0 – 18,000	22	1 – 14	15 – 28	1 – 28	6.4
20.	Ren *et al.*, 2015	Pig defensin and fly-AMP	CAP	0 – 1,000	21	1 – 15	16 – 28	1 – 28	8.24

Table 1. Studies Included in the Meta-analysis of the effect of Anti-microbial Peptide on the Growth Performance in Pigs (continued)

No.	Reference	Antimicrobial peptide	Form	Dosage	Initial age[1)]	Rearing period			IBW
						Phase 1[2)]	Phase 2[2)]	Total[2)]	
21.	Shan *et al.*, 2007	Lactoferrin	SAP	0 – 1,000	28	–	–	1 – 30	7.1
22.	Shi *et al.*, 2017	Pig defensin and fly-AMP	CAP	0 – 400	–	1 – 14	15 – 28	1 – 28	10.6
23.	Sun *et al.*, 2009	Shrimp low molecular peptide	CAP	0 – 3,733	21	1 – 10	–	1 – 21	7
24.	Tang *et al.*, 2009	CipB-lactoferricin-lactoferrampin	SAP	0 – 98	21	–	–	1 – 21	5.44
25.	Tang *et al.*, 2012	CipB-lactoferricin-lactoferrampin	SAP	0 – 98	21	–	–	1 – 21	5.9
26.	Tang *et al.*, 2016	Pig β-defensin 2	SAP	0 – 1	21	–	–	1 – 21	5.83
27.	Wan *et al.*, 2016	Recombinant plectasin	SAP	0 – 60	24	–	–	1 – 21	7.67
28.	Wang *et al.*, 2011	Antibacterial peptide	SAP	0 – 10	28	–	–	1 – 28	8.4
29.	Wu *et al.*, 2012	Cecropin AD	SAP	0 – 400	21	1 – 12	13 – 19	1 – 19	6.76
30.	Xiao *et al.*, 2013a	Composite antimicrobial peptide	CAP	0 – 4,000	28	1 – 15	16 – 30	1 – 30	–
31.	Xiao *et al.*, 2013b	Composite antimicrobial peptide	CAP	0 – 4,000	28	1 – 15	16 – 30	1 – 30	–
32.	Xiao *et al.*, 2015	Composite antimicrobial peptide	CAP	0 – 4,000	28	1 – 15	16 – 30	1 – 30	–
33.	Xiong *et al.*, 2014	Composite antimicrobial peptide	CAP	0 – 3,000	24	–	–	1 – 32	7
34.	Xiong *et al.*, 2019	Lysozyme	SAP	0 – 100	7	1 – 14	–	1 – 14	1.2
35.	Yoon *et al.*, 2012	AMP-A3	SAP	0 – 90	21	1 – 14	15 – 28	1 – 28	5.76
36.	Yoon *et al.*, 2013	AMP-P5	SAP	0 – 60	21	1 – 14	15 – 28	1 – 28	6.22
37.	Yoon *et al.*, 2014	AMP-A3 and AMP-P5	SAP	0 – 60	21	1 – 14	15 – 28	1 – 28	5.9
38.	Yu *et al.*, 2017	Microcin J25	SAP	0 – 2	25	1 – 15	16 – 28	1 – 28	7.98
39.	Yuan *et al.*, 2015	Pig defensin and fly-AMP	CAP	0 – 1000	21	–	–	1 – 28	–
40.	Zhou *et al.*, 2010	Enzymolytic soybean small peptide	CAP	0 – 18,568	28	–	–	1 – 28	9.08
41.	Zou *et al.*, 2019	Lysozyme	SAP	0 – 100	–	–	–	1 – 30	19.8

AMP, antimicrobial peptide; CAP, composite antimicrobial peptide; IBW, initial body weight (Kg); SAP, single antimicrobial peptide; 1) Age at initial experiment (days from birth).

2009). The role of epithelial tissue as a protective wall has a significant role in the absorption of AMP in pigs. If AMP synergizes with thickened epithelial cells, the concentration of pathogenic microbes can be suppressed (Tang *et al.,* 2016). Several types of T-cells secreted in the intestinal tissue are IL-2, IL-4, IL-5, IL-10, and interferon-γ (Tang *et al*., 2016). This T-cell network secretes cytokinin if the intestinal condition is healthy when AMP has synergized in the pig's body. Previous research of Tang *et al*., (2012) reported that increasing the dose of synergistic AMP administration increased the average body weight growth of 13.3% (1st phase) and 29.3% (2nd phase). Furthermore, it is conveyed that the increasing rise in the average body weight tends to feed conversion ratio by 11.5% in phase -1 of pig and phase-2 as much as 15.3% compared to control.

The Effect of AMP on the ADI of pigs

Administering AMP in the form of SCA in the study has consistently increased the average daily feed consumption both on average and maintenance in phase 1 and phase 2 (Yoon *et al.,* 2012; 2013, 2014). Yoon *et al.* (2012) stated , administration of AMP in the form of SCA is relatively stable when the pigmentation system begins to develop in the first maintenance phase until it is effective for 4-5 weeks of use. AMP can be a supporting agent in the intestinal tract of pigs to increase the body's immune system, where pigs are susceptible to stress and disease during the initial rearing period. *Zhou et al.* (2010) reported that the use of AMP in the form of CAP can increase the average daily feed consumption by 18, 25, and 38% at optimal levels, particularly 15% of administration in the feed. The use of AMP in the form of CAP from soybeans still contained high anti-nutritional substances; thus, it is necessary to treat it using protease enzymes. Zhou *et al.* (2010) reported that the increasing level of AMP in the form of CAP that the higher the feed consumption in pigs is correlated with the increased body weight.

The Effect of AMP on the Diarrhea Ratio and Survival Rate of Pigs

Feng *et al.* (2020) reported, the anti-microbial peptide can reduce diarrhea ratio a half number compared to control. In linear, the feed intake had increased twice daily in pig after offering anti-microbial peptide in feed. The high incidence of diarrhea and mortality are the problems during rearing period. Diarrhea is not only severely retarded the growth of pig during the early growth period but seriously and leads to increase the mortality of pig (Feng *et al.,* 2020). Wu *et al.* (2012) reported that pig fed diet containing anti-microbial-peptide until 400 mg/kg can reduce diarrhea ratio and increase linearly the average daily gain in growing phase of pig. The lower diarrhea ration made improvement on the immunological organ and intestinal tract over 80% of the immune cells of the body's immune system, which later play a crucial role in the defense system (Feng *et al.,* 2020). The diarrhea caused by *Escherichia coli* in the intestinal of pig (Xiong *et al.,* 2014). This disease occurs in the first weeks after weaning and is characterized by sudden death or diarrhea, dehydration, and growth retardation in pig. In addition, many stress factors are associated with the weaning period, such as removing piglet from their sow, changes in diet, adapting to new environments, mixing of pigs from different farms and physiological changes in the small intestine those could be the negatively impact response (Xiong *et al.,* 2014). The mode of action from anti-microbial peptide in the body can be seen in the Figure 1.

CONCLUSION

The result provided by this meta-analysis demonstrates the enhancement of overall performance of pig supplemented with anti-microbial peptide as replacement of antibiotics growth promoters (AGPs). Both form and dosage of the anti -microbial peptide increased the growth performance of the pig and could be the dose dependent.

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