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Effect of Using Peptide as a Replacement of Antibiotic Growth Promoters on Pigs: a Systematic Review and Meta-regression

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ABSTRACT

A systematic review and meta-regression were done to investigate the effect of using peptide as a replacement of antibiotic growth promoters on pig. A dataset was created based on an algorithm for peer-reviewed articles published from 2004 to 2019. The peer-reviewed published articles were evaluated strictly following the eligibility criteria for inclusion. Meta-regression was performed using a non-linear mixed model library provided by R Studio 4.1.1 software. A structure algorithm was constructed using 'magick', 'ggplot', 'ggplot2' and 'cowplot' add-ons to create a meta-regression. In this study, meta-regression between year of publication and number of pigs included in the experiments was associated with growth performance and diarrhea with $p = 0.032$ and $p < 0.163$, respectively. Meanwhile, the source of peptide intercepts for these parameters were 38.33 ($p = 0.052$) and 48.44 ($p = < 0.071$), respectively. The scientific evidence from the meta-analysis based on the in-vivo studies demonstrates that both form and dosage of the anti-microbial have a beneficial effect on pigs.

Introduction

Antibiotic Growth Promoters (AGPs) has been used worldwide for more than 40 years. Depending on the use of antibiotics in feed, several aspects must be considered 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* (Sjofjan *et al*., 2021a; Sjofjan *et al*., 2021b). With the development of animal industry, 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 for artificial antibiotics, particularly the technology of the utilization of antimicrobial peptides. This technology has been implemented since the European Union banned antibiotics as feed additives. The ban on antibiotics 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; Sjofjan *et al*., 2021c). This prohibition's impact has made many researchers, business actors, industry players, and breeders searching for alternatives to replace antibiotics, one

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of which is the peptide.

Peptides are molecules produced by cells in the tissues of living things that act as the body's defense system. The peptide can neutralize endotoxin produced by gram-negative bacteria. Based on the form of administration in pigs, peptide 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 age for age and initial body weight is 22 days and 6.34 kg. Research conducted by Yoon *et al.*, (2014) 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.*, (2013a) 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. One method of answering this inconsistent result is to utilize statistical meta-analysis techniques. Therefore, this study aimed to summarize and determine the effect of administering peptides on growth performance in pigs through systematic review and meta-regression studies from various sources of scientific publications.

Materials and methods

Dataset development

Raw data from selected articles were extracted if articles reported the use of an anti-microbial peptide in pig. Peer-reviewed published articles were chosen and carefully evaluated following Systematic Review Center for Laboratory Animal Experimentation (SYRCLE') protocols. An algorithm was chosen in order to search peer-reviewed published articles in the following websites:

Science direct (www.sciencedirect.com/); Medline (www.nlm.nih.gov/medline/medline_overview.html); PubMed (https://pubmed.ncbi.nlm.nih.gov/) and other scientific publishing platforms. The period set for appropriate published articles was from 2004 to 2019, and the following keywords were used: 'pig', 'performance', 'peptide', and 'survival'. In each article evaluated, we also evaluated reference lists to search for potentially relevant articles that might have been missed during the initial search.

Development of the dataset

Peer-reviewed published articles were selected based on the PICOS (population, intervention, comparison, outcomes, and study selection) model. Criteria for article to be included in data-base were as follows: (a) article was published in a peer-reviewed journal with range 2004-2019, (b) the pig were modern-controlled-trial environment and management, (c) peptide treatment excluded from the database, (e) the articles written consistent in English were considered in studies, (d) The parameters included in these 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 was converted into same unit.

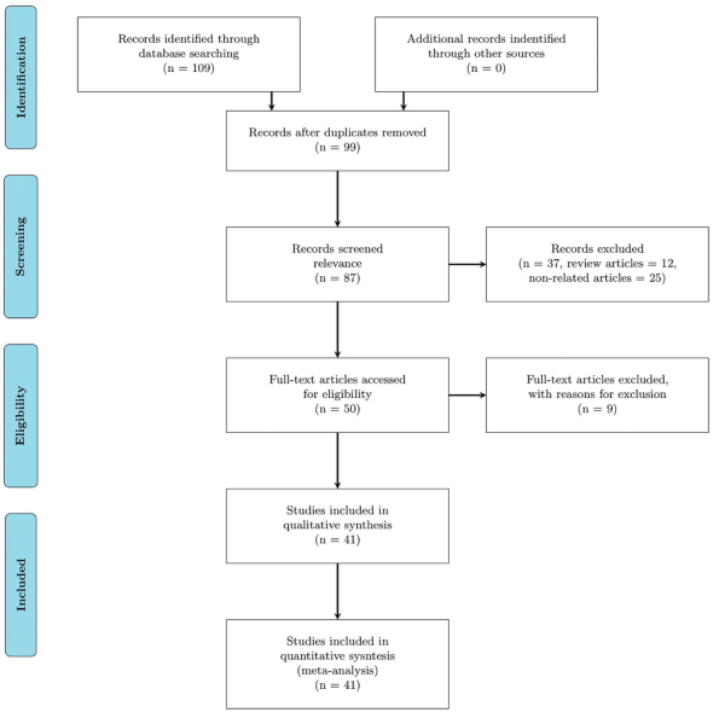

Fig. 1. The diagram of the selection of article followed PRISMA-P (Shamseer *et al.*, 2015)

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 subjected to an online tools WebplotDigitizer method. The final dataset was consisted of 41 in vivo studies. While the summary of the used final dataset is presented in Table 1. The details for the study selection included in meta-analysis are provided in Figure 1.

Data analysis

The development of the studies was taken as the random effects, while the concentrations supplementation were taken as the fixed effect. The mathematical model used were following (Jin *et al.*, 2009; Ren *et al.*, 2015).

1) $Y_{ij}=\beta_0+\beta_1 Level_{ij}+Experiment_i+Experiment_i\ Level_{ij}+e_{ij}$

2) $Y_{ij}=\beta_0+\beta_1 Level_{ij}+\beta_2\ Level^2_{ij}+Experiment_i+Experiment_i\ Level_{ij}+e_{ij}$

Where: Y_{ijk} = dependent variable, μ = averages all studies, si = 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 Y_{ij} = dependent variable; B_0 = overall intercept across all studies (fixed effect); B_1 = linear regression coefficient of Y on X (fixed effect); B_2 = quadratic regression coefficient of Y on X (fixed effect); Xij = value of the continuous predictor variable (peptide levels); s_i = value of random effect of study i; b_i = random effect of study on the regression coefficient of Y on X in study i; and e_{ij} = the unexplained residual error.

In the end, we conducted a meta-regression to explore the source of hedges'd in each experimental effect. Meta-regression present relationship and gap between years of publication, number of pig included in the experiments and duration of studies, and source of fiber used as covariates. A meta-regression was performed using the restricted maximum likelihood (REML) (Metareg, R Studio) as follows (Harrer *et al.*, 2019).

Table 1. Studies included in the meta-regression of the effect of anti-microbial peptide on the growth performance of the pig.

No.	Reference	Source of 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)	Serum 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	Hu *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.* (2)	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)	Serum 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
21	Shan *et al.* (2007)	Lactoferrin	SAP	0 – 1,000	28	–	–	1 – 30	7.1
22	Shi *et al.* (2018)	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.* ( )	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.*(2006)	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 defensing 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

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

1) $\theta k = \theta + \beta_{1xi} + \epsilon k + \zeta k$

θk = observed effect size, θ = identical with the true overall effect size, where ϵk is the sampling error through which the effect size of a study deviates from its true effect, ζk is denotes that even the true effect size of the study is only sampled from an overarching distribution of effect sizes.

Results

Based on the results of the meta-regression, administering peptide increased (p <0.05; quadratic) body weight, average daily gain (ADG), and average daily intake (ADI) significantly, and significantly decreased (p <0.05; quadratic) feed conversion ratio (FCR) of pigs in phase 1 (Table 2). In phase 2, the administration of antimicrobial peptide (AMP) significantly increased (p <0.05, squared) body weight, but significantly 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 significantly (p <0.05; quadratic) increased body weight and ADG while the FCR decreased (p <0.05; quadratic). In the total phase, body weight significantly 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) was not significant 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 significantly increased (p <0.05; quadratic) growth performance (e.g., body weight, ADG, and ADI) while FCR decreased significantly (p <0.05; linear) in phase 1 (Table 4). 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. In this study, meta-regression between year of publication and number of pig included in the experiments was associated with growth performance and diarrhea with p = 0.032 and p < 0.163, respectively. Meanwhile, the source of peptide (AMP) intercepts for these parameters were 38.33 (p = 0.052) and 48.44 (p = < 0.071), respectively (Table 5).

Table 2. Regression of the dosage in the meta-analyses of the effect of anti-microbial peptide on the growth performance of the pig

No.	Response	Unit	M	N	Parameter estimates				Model estimates			Interpretation		
					Int.	SE Int.	Slope	SE Slope	p-Value	RMSE	AIC[1)]	Trend	X	Y
1	Body weight	g	Q	146	9.83	299	0.04	0.007	<0.001	1.75	2,435	Max.	38.95	10.61
2	ADG	g/h/d	Q	146	229	9.49	0.002	0.0005	<0.001	1.67	1,574	Max.	40.31	288
3	ADI	g/h/d	Q	144	324	16.01	0.003	0.0006	<0.001	1.73	1,642	Max.	38.9	394
4	FCR		Q	144	1.45	0.045	-3.11	7.43	<0.001	1.93	-25.4	Neg.		
5	Body weight	g	Q	116	15.6	454	0.045	0.02	0.028	1.68	2,052	Max.	22.79	16.17
6	ADG	g/h/d	L	116	431	12.7	-0.0008	0.0003	0.013	1.51	1,263	Neg.		
7	ADI	g/h/d	L	114	710	25.6	-0.001	0.0005	0.009	1.67	1,364	Neg.		
8	FCR		L	114	2	0.032	5.34	1.4	0.7	1.75	-36.6	Pos.		
9	Body weight	g	Q	178	15.9	583	0.071	0.024	0.004	2.27	3,248	Max.	23.44	16.74
10	ADG	g/h/d	L	181	339	11.9	0.00056	0.0006	0.36	3.51	2,117	Pos.		
11	ADI	g/h/d	L	179	542	25.2	0.0006	0.0006	0.27	2.33	2,186	Pos.		
12	FCR		L	179	1.59	0.034	-1	2.44	0.66	3.97	89.6	Neg.		
13	Diarrhea ratios	%	L	66	12.9	2.83	-0.0002	0.0007	0.76	1.63	544	Neg.		
14	Survival rate	%	Q	15	90.2	1.61	0.003	7e-005	<0.001	1	70.4	Max.	2.29	94.5

Note: ADG, average daily gain; ADI, average daily intake; AIC, akaike information criterion; FCR, feed conversion ratio; Int., intercept; L, linear; M, model; Max., maximum; Min, minimum; N, number of data; Neg., negative; Pos., positive; Q, quadratic; RMSE, root mean square errors; SE, standard error; X, optimal doses (mg/Kg of diet); Y, optimal output of the response variable; 1) AIC is the estimated value of the goodness of the model.

Table 3. Regression of the dosage in the meta-analyses of the effect of single anti-microbial peptide on the growth performance of the pig

No.	Response	Unit	M	N	Parameter estimates				Model estimates			Interpretation		
					Int.	SE Int.	Slope	SE Slope	p-Value	RMSE	AIC[1)]	Trend	X	Y
1	Body weight	g	Q	42	10.27	720	8.23	1.5	<0.001	1.33	686	Max.	211	11.1
2	ADG	g/h/d	Q	42	243	22.4	0.544	0.108	<0.001	1.27	454	Max.	217	302
3	ADI	g/h/d	Q	40	388	28.5	0.36	0.111	0.004	1	439	Max.	230	429
4	FCR		Q	40	1.61	0.08	-0.002	0.00063	0.004	1.35	37.5	Min.	213	1.39
5	Body weight	g	Q	35	16.13	998	16.7	3.21	<0.001	1.08	604	Max.	214	17.92
6	ADG	g/h/d	Q	35	389	30.4	0.588	0.124	<0.001	0.96	390	Max.	230	457
7	ADI	g/h/d	L	33	715	42	0.162	0.126	0.215	1.12	392	Pos.		
8	FCR		Q	33	1.74	0.04	-0.001	0.00062	0.008	1.3	20	Min.	221	1.54
9	Body weight	g	Q	59	16.19	1420	15.9	4.6	0.001	1.99	1.09	Max.	212	17.89
10	ADG	g/h/d	L	62	344	29.5	0.206	0.146	0.166	2.26	772	Pos.		
11	ADI	g/h/d	L	60	609	58.1	0.166	0.137	0.233	1.66	768	Pos.		
12	FCR		L	60	1.76	0.06	-0.0007	0.00058	0.192	2.75	71	Neg.		

Note: ADG, average daily gain; ADI, average daily intake; AIC, akaike information criterion; FCR, feed conversion ratio; Int., intercept; L, linier; M, model; Max., maximum; Min, minimum; N, number of data; Neg., negative; Pos., positive; Q, quadratic; RMSE, root mean square errors; SE, standard error; X, optimal doses (mg/Kg of diet); Y, optimal output of the response variable; 1) AIC is the estimated value of the goodness of the model.

Table 4. Regression of the dosage in the meta-analyses of the effect of composite anti-microbial peptide on the growth performance of the pig.

No.	Response	Unit	M	N	Parameter estimates				Model estimates			Interpretation		
					Int.	SE Int.	Slope	SE Slope	p-Value	RMSE	AIC[1)]	Trend	X	Y
1	Body weight	g	Q	104	9,567	303	0.04	0.006	<0.001	1.99	1.71	Max.	39.02	10.3
2	ADG	g/h/d	Q	104	216	9.48	0.002	0.0004	<0.001	1.5	1.1	Max.	40.3	277
3	ADI	g/h/d	Q	104	296	17.5	0.003	0.0006	<0.001	1.68	1.2	Max.	38.7	368
4	FCR	-	L	104	1.41	0.054	-3e-006	5.6e-007	<0.001	1.67	-39.8	Neg.		
5	Body weight	g	Q	81	15,206	479	0.046	0.01	0.004	1.15	1.41	Max.	23.04	15,7
6	ADG	g/h/d	L	81	439	13.1	-0.0009	0.0003	0.004	1.31	864	Neg.		
7	ADI	g/h/d	L	81	704	32	-0.001	0.0004	0.004	1.89	966	Neg.		
8	FCR		L	81	1.59	0.041	6.5e-007	1e-006	0.606	1.73	-21.2	Pos.		
9	Body weight	g	Q	119	15,497	493	0.07	0.01	<0.001	1.41	2.1	Max.	23.5	16,3
10	ADG	g/h/d	Q	119	326	10	0.002	0.0006	<0.001	1.39	1.2	Max.	24	360
11	ADI	g/h/d	L	119	502	22.2	0.0007	0.00042	0.089	1.76	1.37	Pos.		
12	FCR	-	Q	119	1.53	0.04	-6e-006	2.1e-006	0.009	1.63	-34.8	Min.	21.4	1.47
13	Survival rate	%	Q	15	90.2	1.61	0.003	7e-005	<0.001	1	70.4	Max.	2.2	94.5

Note: ADG, average daily gain; ADI, average daily intake; AIC, akaike information criterion; FCR, feed conversion ratio; Int., intercept; L, linear; M, model; Max., maximum; Min, minimum; N, number of data; Neg., negative; Pos., positive; Q, quadratic; RMSE, root mean square errors; SE, standard error; X, optimal doses (mg/Kg of diet); Y, optimal output of the response variable; 1) AIC is the estimated value of the goodness of the model.

Table 5. Meta-regression of anti-microbial peptide on pig

Co-variable		Growth Performance	Diarrhea ratio
Year of publication	Intercept	32.13	24.55
	p	0.0032	<0.023
	Slope	0.57	13.11
	p	0.034	<0.0017
Numbers of pig included in the experiments	Intercept	8.63	62.11
	p	0.32	<0.163
	Slope	0.12	51.21
	p	0.033	<0.21
Source of anti-microbial peptide used	Intercept	38.33	48.44
	p	0.052	<0.071
	Slope	0.12	71.11
	p	0.017	<0.072

Discussion

The use of peptides 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 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). Peptide from animals has consistently had a positive effect on the increasing growth of pigs (Berding *et al.*, 2016; Boudry *et al.*, 2007; Cutler *et al.*, 2007). Positive results are also reported in the research of (May *et al.*, 2012; Long *et al.*, 2016) that the use of peptide 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 (May *et al.*, 2012; Long *et al.*, 2016).

The use of peptide 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 pepsin enzyme in the pig blood. Peptide that enters the blood is responsible for enhancing immune function and increasing the intestinal mucosal wall, when pigs reach the rearing age of 21 days (Tang *et al.*, 2009). The role of epithelial tissue as a protective wall has a significant role in the absorption of AMP in pigs. If peptide 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) stated that increasing the dose of synergistic AMP administration increased the average body weight growth of 13.3% (1st phase) and 29.3% (2nd phase). According to Yoon *et al.* (2014), 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.* (2011) 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 retardation in pig. Small intestines are known to negatively impact response (Xiong *et al.*, 2014).

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 increased the growth performance of the pig.

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Conflict of interest

The authors declared that they have no conflict of interests exist.

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