R. Bras. Zootec., 53:e20210186, 2024
https://doi.org/10.37496/rbz5320210186

Non-ruminants
Full-length research article

Revista Brasileira de Zootecnia

Brazilian Journal of Animal Science
e-ISSN 1806-9290
www.rbz.org.br

Effects of administering phytogenic additives and antibiotics to unchallenged nursery piglets: A meta-analytic approach

Letícia Galvão Matoso[1], Vitoria Weege[1], Charlise Campos Primieri[1], Anna Paula Holzmann Mass[1], Edilson Andrade[1], Cheila Roberta Lehnen[1]*

[1] Universidade Estadual de Ponta Grossa, Departamento de Zootecnia, Grupo de Pesquisa BioModel, Ponta Grossa, PR, Brasil.

***Corresponding author:**
cheilalehnen@gmail.com

Received: October 27, 2021
Accepted: February 3, 2023

How to cite: Matoso, L. G.; Weege, V.; Primieri, C. C.; Mass, A. P. H.; Andrade, E. and Lehnen, C. R. 2024. Effects of administering phytogenic additives and antibiotics to unchallenged nursery piglets: A meta-analytic approach. Revista Brasileira de Zootecnia 53:e20210186.
https://doi.org/10.37496/rbz5320210186

ABSTRACT - A meta-analysis was employed to assess the effects of phytogenic feed additives and antibiotics on the performance and intestinal morphometry of unchallenged weanling pigs. The database included 41 articles published between 2004 and 2017, comprising 5,197 unchallenged nursery piglets. Piglets had 7.7 to 13.8 kg body weight and were assessed at 27.3 to 47.8 days of age, distributed into 156 experimental groups. All treatments were categorized into negative control, phytogenic additive (PA), and antibiotics (ATB) groups. The meta-analysis followed two sequential analyses: graphical and variance-covariance. Age and body weight were the factors that highly influenced the model. Piglets that received antibiotics had a higher (12.2%) daily weight gain than piglets in the control group. Phytogenic additives in diets enhanced intestinal morphometry in unchallenged piglets. Antibiotics increased (by 12.7%) the crypt depth of jejunum in comparison to the control treatment. Animals on PA had an 11.1% increment in villus height:crypt depth ratio than those on antibiotics. Phytogenic additives and antibiotics boost nursery piglet performance. Antibiotics advances the performance of unchallenged nursery piglets, but increases crypt depth in the jejunum. Performance of nursery piglets is better with combined phytogenic additives than with the isolated use of plant extracts.

Keywords: feed additive, piglet nutrition, plant extract, weaning piglets

1. Introduction

Weaning in piglets is considered a crucial phase, since it exposes animals to external stress. Salient factors are of social order, including the separation of the mother from piglets, social hierarchy after mixing batches; environmental factors, including alterations in housing and temperature; and physiological factors, such as the change from a liquid to solid diet (Campbell et al., 2013). During the first week in the nursery, piglets lower their feed intake, negatively affecting weight gain. Changes in the physical form and chemical composition of the diet modify the architecture of villi and may reduce digestion and absorption of nutrients (Camilleri et al., 2012; Wang et al., 2021). These scenarios can impair piglet performance and gut health. Antibiotics have been the best approach to mitigate these negative impacts on performance (Fang et al., 2009), and they are administered via diet to swine herds as a preventive treatment (Dutra et al., 2021). However, some researchers have found no differences in the performance of unchallenged piglets fed diets containing antibiotics (Long et al., 2018).

Penicillin, tetracyclines, and macrolides are antibiotics typically used in pig production (Lekagul et al., 2019). Colistin, tylosin, and avilamycin are often used as feed additives in the production of pigs; they are especially useful in piglets challenged health-wise (with the presence of pathogens) or environment-wise (with heat stress and suboptimal housing) (Kumar et al., 2020; Dutra et al., 2021). However, owing to the intensive use of antibiotics in current production systems, bacterial resistance to antibiotics may develop, posing a threat to humans (Zhai et al., 2018). Consequently, many countries have banned or restricted the use of antibiotics as growth promoters in animal production (Rahman et al., 2022). Based on the adopted measures, substitutes for antibiotics, including phytogenic additives, have been researched.

Phytogenic feed additives are plant-derived components, such as herbs, spices, essential oils, and saponins. An array of plant extracts and active substances have been investigated in poultry and swine feeds. Many studies have reported positive results pertaining to the performance and intestinal health of piglets after being administered such feed additives (Hanczakowska and Swiatkiewicz, 2012; Santana et al., 2015; Omonijo et al., 2018; Zhai et al., 2018). Phytogenic additives have complicated mechanisms of actions that are quite obscure to the scientific community (Zhai et al., 2018; Wang et al., 2021). Additionally, the effects are dependent on the botanical source, concentrations of active compounds, diet composition, animal age, and presence or absence of sanitary challenges. The integration of this information is challenging. In this context, the meta-analytic approach is the most suitable to collate and synthesize previously published results on a subject with novel conclusions (Sauvant et al., 2020). Therefore, in this meta-analysis, we aimed to evaluate the effects of phytogenic and antibiotic additives on the performance and intestinal morphometric responses in unchallenged piglets.

2. Material and Methods

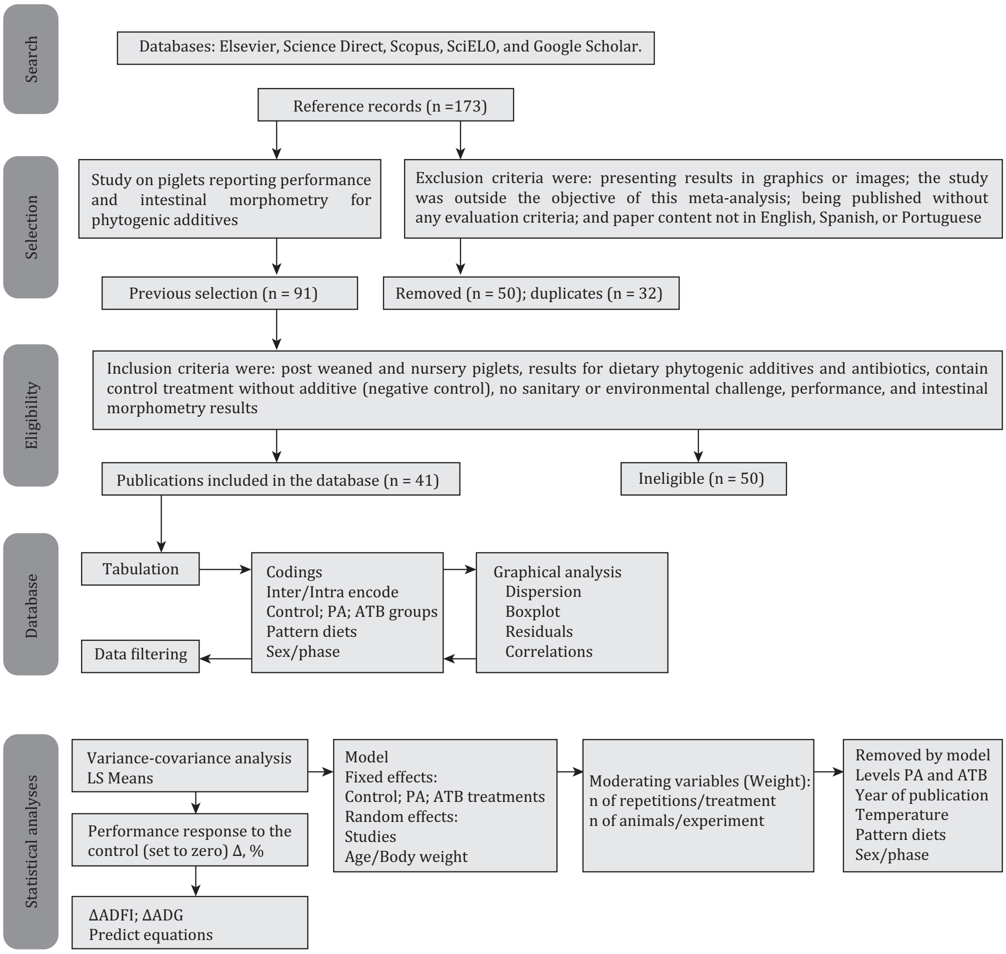
2.1. Systematization of information

Indexed publications based on *in vivo* experiments involving unchallenged piglets fed diets supplemented with phytogenic additives in the nursery phase were chosen from the digital databases Elsevier, ScienceDirect, Scopus, SciELO, and Google Scholar. Only studies reporting the performance and intestinal morphometry were considered in the analysis. The selected studies were critically analyzed in terms of their relevance and quality to the meta-analysis objectives, including the experimental design, treatments, variables, and data analysis used in the studies. Eligibility criteria were post-weaned and nursery piglets, results for dietary phytogenic additives and antibiotics, containing a negative control without additives, no sanitary or environmental challenge, performance, and intestinal morphometry results. The outcome of a single study, i.e., if herbal extract was beneficial, was not considered as a criterion for inclusion in this database. From 91 publications, only 40 were considered in the database. The following types of publications were excluded: studies with only graphical results, studies outside the objective of this meta-analysis, publications without any evaluation criteria, and content not in English, Spanish, or Portuguese (Figure 1).

2.2. Database management, coding, and data filtering

A database with information characteristic to each selected study was created employing Microsoft Excel (2013). The tabulated data referred to bibliographic aspects (authors, year, journal, country, and institution of origin), experimental characteristics (experimental design, diet ingredients, inclusion levels, type and form of phytogenic additives and antibiotics, inclusion levels in the diet, nutritional composition, ambient temperature, age, and weight of piglets), and the variables evaluated (growth performance related to average daily feed intake (ADFI), average daily weight gain (ADG), feed conversion ratio (FCR), and intestinal morphometry of gastrointestinal tract segments).

Graphical evaluation was conducted to explore the data distribution and obtain a global perspective of its coherence and heterogeneity. Through this analysis, hypotheses and the statistical model were established (Lovatto et al., 2007). Dependent and independent variables definition and codification of the data for the analysis of inter-and intra-experimental effects were conducted according to Sauvant et al. (2005), Lovatto et al. (2007), and Remus et al. (2014). Sequential numbers were utilized to encode every single study (general encoding), single treatment within a study (inter encoding wherein,



PA - phytogenic additives; ATB - antibiotics; LS-Means - least-square means; ΔADFI - average daily feed intake variation; ΔADG - average daily gain variation.

Figure 1 - Flow diagram of applied methodology.

each treatment received a sequential number concatenated to the previously given study code), and encode repeated measures for different intervals or dose when available (intra encoding). Treatments were grouped into negative control (no additives), phytogenic additives (PA), and antibiotics (ATB). Diet patterns were encoded as corn–soybean meal diet (CSBM) and milk byproduct, fish meal and corn–soybean meal diet (MFCSB). Additional encodings were done to facilitate graphical and statistical analysis of the database.

2.3. Database description

The database contained 41 studies published in journals during 2004–2017 (mode:2010). It comprised 5,197 unchallenged nursery piglets, with 7.7 to 13.8 kg body weight (BW) and were assessed at 27.3 to 47.8 days of age, distributed into 156 experimental groups. The experimental duration was 20.6 days (minimum five and maximum 50 days). The data were dispersed across 324 rows and 98 columns. Most studies stemmed from Brazil (50%), Europe (30%), North America (10%), and Asia (10%). The most extensively used phytogenic additive in the selected studies was oregano (43.0%), thyme (24.5%), pepper (18.1%), and cinnamon (18.0%). In 54% of the studies, there was a group of antibiotics, 40% used colistin. Barrow piglets accounted for 71.4% of the piglets, female piglets accounted for 3.2%, and 25.4% of the studies did not report sex details. Descriptive statistics of the variables for nursery piglets receiving diets supplemented with phytogenic additives and antibiotics are represented in Table 1.

Table 1 - Database description of selected studies in the meta-analysis of phytogenic feed additives and antibiotics for unchallenged nursery piglets

N	Authors	Country	BWi (kg)	BWf (kg)	Pattern diets	T (°C)	PA	ppm	ATB	ppm
1	Barroca (2011)	Brazil	5.67	16.10	MFCSB	16.9-29.3	C, O, Ro, P	200	C	60
2	Branco et al. (2011)	Brazil	8.00	29.60	CSBM	-	AN, ANs, Thy, O, E, Gi	200, 400, 600	T	2000
3	Caldara et al. (2009)	Brazil	5.99	9.17	CSBM		Ga, O	5,000; 5,000	N	110
4	Colina et al. (2001)		5.20	14.37	MFCSB	25	Y	125		
5	Costa et al. (2007)	Brazil	7.12	18.57	MFCSB	-	Cl, O	420, 420, 840		
6	Costa et al. (2011)	Brazil	6.08	21.64	MFCSB		Thy, C, E, Me, Ech, G, P	500	BT	1500
7	Namkung et al. (2004)	Canada	4.90	11.97	CSBM	-	C, Thy, O	7,500	L	110
8	Halas et al. (2011)	Hungary	7.90	17.07	MFCSB	-	O, Cl, C	250	A	40
9	Hanczakowska and Swiatkiewicz (2012)	Poland	7.96	14.31	CSBM	-	S, LB, Ne, Ech	500		
10	Li et al. (2012)	China	8.37	28.53	CSBM	-	Tm, Cn	180,000	CL, C, K	280
11	Lovatto et al. (2005)	Brazil	-	-	CSBM	-	Ga	500; 1,500	C	250
12	Manzanilla et al. (2006)	Barcelona	6.05	8.63	MFCSB	25-29	Ca, Cn, P	10,000	A, BT	1700
13	Mueller et al. (2012)	Germany	9.60	20.57	CSBM	21-26	Br, Cu, Thy, O, Ro	150, 535, 373, 282, 476		
14	Oetting et al. (2006)	Brazil	7.84	17.96	MFCSB	-	Cl, Thy, O, Eu, Ca	700; 1,400; 2,100	B, O, C	150
15	Pedroso et al. (2005)	Brazil	-	9.62	MFCSB		Cl, O, Thy	700; 1,400; 2,100	B, C, O	50
16	Santana et al. (2015)	Brazil	7.17	27.74	MFCSB	-	SP, Ro, B	50,000	C	40
17	Suzuki et al. (2008)	Brazil	6.94	32.39		-	Ca, Tm	2,000		2000
18	Toseti et al. (2013)	Brazil	9.00	13.95	-		Pr	3,500; 15,000	B	7
19	Utiyama et al. (2006)	Brazil	6.04	19.83	MFCSB		Ga, Cl, C, Thy, E	500	B, O	100
20	Vale et al. (2010)	Brazil	7.20	-	CSBM	-	Thy, Le, E, Ga, AN, Ans, Gi, O	200, 400, 600	T	20
21	Zangeronimo et al. (2011)	Brazil	7.40	27.59	MFCSB	-	C, Cl, Ga, O, Cm, E, P	500, 100	C, ZO	30

Continues...

BWi - initial body weight; BWf - final body weight; Pattern diets: CSBM - corn/soybean meal diet; MFCSB - milk byproducts, fish meal in corn/soybean meal diet; T (°C) - environment temperature; ppm - level of addition or inclusion in diets; PA - phytogenic additives: AN - anise; ANs - star anise; B - boldo; Br - broccolis; C - cinnamon; Ca - carvacrol; Cl - clove; Cm - chamomile; Cn - cinnamaldehyde; Cu - curcuma; E - eucalyptus; Ech - echinacea; G - ginger; Ga - garlic; Gi - ginepro; LB - lemon balm; Le - lemon; Me - melaleuca; Ne - nettle; O - oregano; P - pepper; Pr - propolis; Ro - rosemary; S - sage; SP - sweet potato; Thy - thyme; Tm - thymol; Y - yucca; ATB - antibiotics: A - avilamycin; B - zinc bacitracin; BT - sodium butyrate; C - colistin; CL - chlorotetracycline; K - kitasamycin; L - lincomycin; N - neomycin; O - olaquindox; T - trisulfin; ZO - zinc oxide.

Table 1 (Continued)

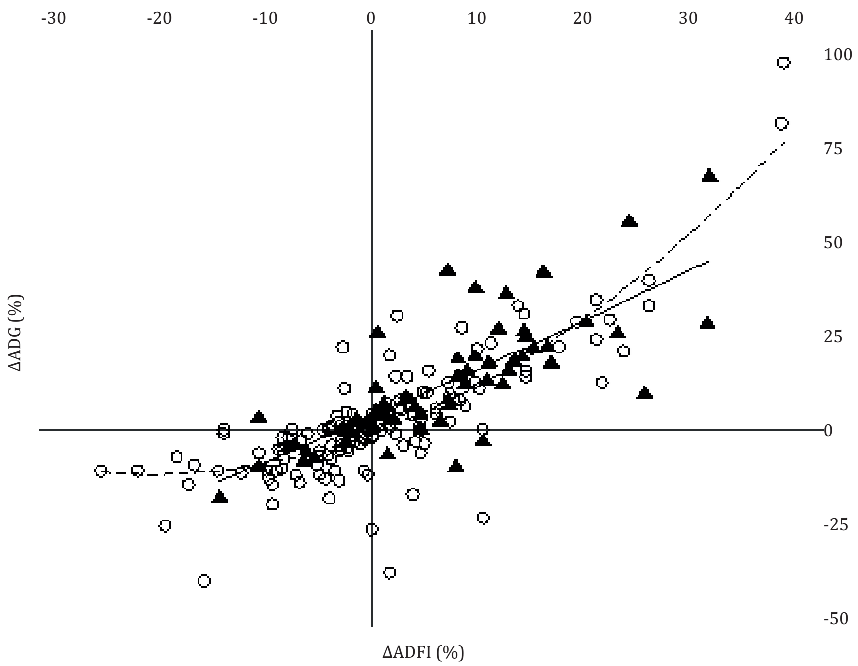
N	Authors	Country	BWi (kg)	BWf (kg)	Pattern diets	T (°C)	PA	ppm	ATB	ppm
22	Václavková and Bečková (2008)	Czech Republic	8.22	-	-	-	Q	12,500		
23	Ding et al. (2011)	China	5.86	10.32	-	27	CHMD	500; 10,000; 15,000		
24	Gräber et al. (2014)	Saxony	8.43	23.53	-	22-29	Agr	870; 8,700		
25	Clouard and Val-Laillert (2014)	France	8.33	20.22	CSBM	24.6-25	S, Ore, Air	100,000; 60,0000; 50,000		
26	Liu et al. (2013)	Geneva	7.64	-	MFCSB	-	P, Ga, Cu,	10; 10; 10		
27	Maenner et al. (2011)	Germany	5.46	5.85	MFCSB	-	AN, Mi, Cl, C	86.3; 7.74		
28	Silva Júnior (2016)	Brazil	8.10	13.10	-	-	Cl, Tm, P	3,000	C	40
29	Ikeda (2015)	Brazil	8.03	12.40	MFCSB	-	Pr	4,000	CH	120
30	Neill et al. (2006)	USA	5.90	16.55	MFCSB	-	O	37.5	N	154
31	Cho et al. (2012)	Korea	7.17	26.93		-	Ta, Jap, Hou, Tree	1,000; 500; 1,000; 1,000		
32	Henn et al. (2010)	Brazil	9.83	19.81		-	O	30	B	50
33	Yan et al. (2012)	Korea	7.61	15.96	MFCSB	30	Oa, Thy, Cu, P, G	250	AP	30
34	Ramos et al. (2013)	Brazil	6.65	19.02	-	-	Che	10,000		
35	Santos (2010)	Portugal	6.38	22.29	MFCSB	26	Ci, C, E	30,000; 50,000		
36	Lehnen et al. (2012)	Brazil	7.08	10.55	CSBM	-	Ore, Ber	750		
37	Oliveira (2015)	Brazil	6.02	9.36	-	-	Cit	500	Am	20
38	Ortiz-Rueda et al. (2012)	Colombia	6.00	22.13	-	25	Cit	10,000; 20,000; 30,000		
39	Gazola et al. (2016)	Brazil	7.00	-	CSBM	22-31	Pr	15,000		
40	Michiels et al. (2010)	Belgium	6.59	-	MFCSB	-	Ca, Tm	506; 1,883; 494; 1,970		
41	Gois (2014)	Brazil	5.65	15.95	MFCSB	23.5-28.0	Aro	500; 1,000; 1,500	CH	120

BWi - initial body weight; BWf - final body weight; Pattern diets: CSBM - corn/soybean meal diet; MFCSB - milk byproducts, fish meal in corn/soybean meal diet; T (°C) - environment temperature; ppm - level of addition or inclusion in diets, PA - phytogenic additives: Air - flavoring of hot plants; Agr - agrimonia; AN - anise; Aro - aroeira; Ber - bergamot; C - cinnamon; Ca - carvacrol; Che - *Chenopodium ambrosioides*; Cit - citric acid; Cl - clove; Cu - curcuma; E - eucalyptus; G - ginger; Ga - garlic; Hou - *Houttuynia cordata*; Jap - Japanese-honeysuckle; Mi - peppermint; O - oregano; Oa - oats; Ore - orange; P - pepper; Pr - propolis; Q - *Quillaja saponaria*; S - sage; Ta - tamara; Thy - thyme; Tm - thymol; Tree - lacquer tree extract; ATB - antibiotics: Am - amoxylin; AP - apramycin; B - zinc bacitracin; C - colistin; CH - chlorohydroxyquinoline; N - neomycin.

2.4. Statistical analyses

Variance analysis was performed by applying a generalized linear model with covariate adjustment (LS-means). This analytical model included the effects of phytogenic additives and antibiotics (additives), studies (random effects), and random errors. The model also incorporated year of publication, age (initial and final for each evaluation), and BW (on average between initial and final) as random effects. The temperature and dietary patterns could not be measured and were eliminated from the model. The effect of sex (male/female) and year of publication as fixed effects were not significant (P>0.05) and were eliminated from the model. Moderating variables, such as number of repetitions and number of animals per experiment, were used in the analysis of variance. The effects of age and initial BW were examined as covariates employing Fischer's test (P<0.05) and included in the statistical model. Least-square means of inter-experimental data for control, PA, and ATB were calculated by analysis of variance applying a generalized linear model with covariate adjustment. Interactions between age × additive and BW × additive were evaluated for all the parameters. Interactions between PA and ATB were not measured due to limited data availability.

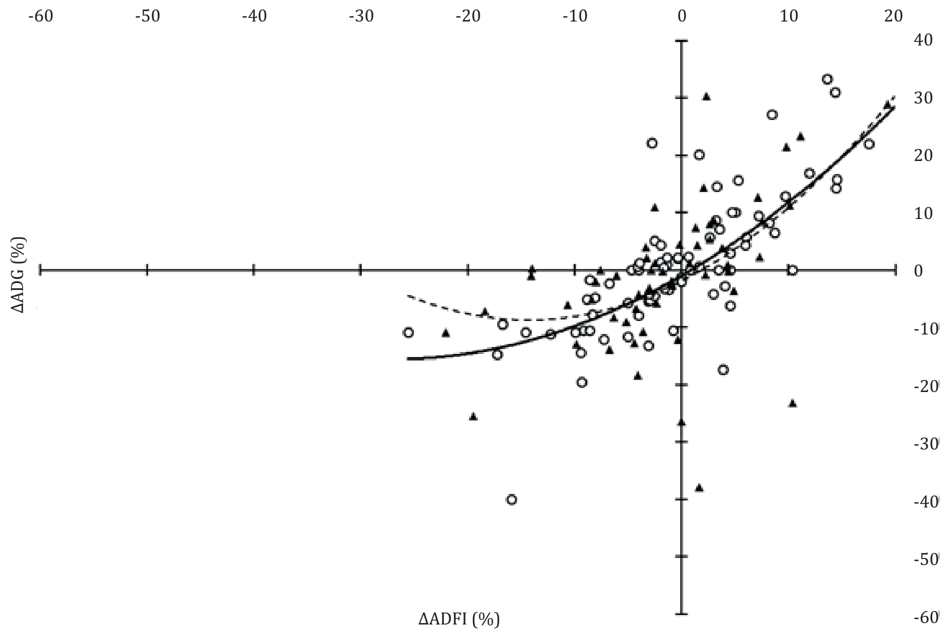
The difference relative to the control (Δ, %), obtained by the intra-experimental variation between the treatments with phytogenic agents or antibiotics compared to the control group, is expressed as a percentage. The relationship between ADFI and ADG was ascertained by expressing the performance response in relation to the control (set to zero). The values are expressed as a percentage change (ΔADFI and ΔADG, respectively), as described by Kipper et al. (2020). This procedure was adopted as it considerably decreases the effect of variation among experiments in the database (Pastorelli et al., 2012). Figures 2 and 3 show calculated values (Δ, %) for each proposed treatment. Prediction



Present calculated values of difference relative (Δ, %) to each treatment. Observed values represented by white circles (○) and equation for phytogenic additives use ($y = 0.969 + 1.038x + 0.025x^2$; $R^2 = 0.69$) represented by dotted line (- - -).
Observed values represented by black triangles (▲) and equation for antibiotics use ($y = 3.660 + 1.231x + 0.002x^2$; $R^2 = 0.58$) represented by a continuous line (–).

Figure 2 - Relationship between average daily gain variation (ΔADG, comparison between negative control and phytogenic additive or antibiotics in piglets) and average daily feed intake variation (ΔADFI), obtained by meta-analysis, of piglets fed diets containing phytogenic additive or antibiotics.

equations were established to evaluate the relationship between ΔADFI and ΔADG. The intercepts of the equations were associated with maintenance requirements, and the slopes were associated with changes in feed conversion. The equations were assessed using regression analysis, and adjusted R^2 was the criterion for selection of the best models. However, owing to the nature of the estimated variables, they were not subjected to validation using the raw data. All analyses were conducted by adopting the MINITAB 19 software (Minitab Inc., State College, USA).



Present calculated values of difference relative (Δ, %) to each treatment. Observed values represented by white circles (○) and equation for phytogenic additive in combined use ($y = 0.991 + 1.079x + 0.019x^2$; $r^2 = 0.77$) represented by dotted line (- - -).
Observed values represented by black triangles (▲) and equation for phytogenic additive in isolated use ($y = -1.240 + 0.951x + 0.033x^2$; $r^2 = 0.67$) represented by a continuous line (–).

Figure 3 - Relationship between average daily gain variation (ΔADG, comparison between negative control and phytogenic additives) and average daily feed intake variation (ΔADFI), obtained by meta-analysis, of piglets fed diets containing herbal extract.

3. Results

In the inter-experimental analysis, feed intake, weight gain, and FCR did not vary (P>0.05) between the use of phytogenic additives and antibiotics in the diets of piglets compared with the control group (Table 2). In the variance analysis, age and BW were the factors that most affected (P<0.001) the model. However, there was no interaction (P>0.05) between these factors. By evaluating the intra-study effects (Δ), we established that the additives had positive (P = 0.04) impact on weight gain, especially piglets that received antibiotics had a higher (12.2%) ADG than those in the control group. Daily weight gain was similar (P = 0.04) in piglets fed diets containing PA and control. Moreover, in FCR, piglets that received ATB had (P = 0.08) a −4.6% lower FCR in the PA and control groups.

Phytogenic additive and ATB in the diets of non-challenged nursery piglets did not change (P>0.05) the villus height of the small intestinal fractions (Table 3). In the morphometry analysis, there was no interaction (P>0.05) between body weight, age, and additives. We also established that the final BW of nursery piglets influenced the height of the duodenum (P = 0.027) and jejunum (P = 0.033) villi. Morphometric parameters were comparable between the PA and control groups. Antibiotics in the diets augmented (P = 0.031) crypt depth in the jejunum. In the intra-study effects (Δ), the ATB effect was more accentuated (P = 0.014) in the jejunum crypt depth, being 12.7% higher compared with the control.

Table 2 - Performance of unchallenged nursery piglets feeding with diets containing phytogenic additives or antibiotics

Additive[1]	n	Performance					
		ADFI (g)		ADG (g)		FCR[3]	
		LS-Means[2]	Δ (%)[3]	LS-Means	Δ (%)	LS-Means	Δ (%)
Control	89	500.9	0.0	326.2	0.0a	1.58	0.0
PA	143	504.6	0.7	340.6	2.6a	1.51	−0.7
ATB	58	528.7	6.7	354.3	12.2b	1.47	−4.6
SD		94.7	7.8	75.6	12.9	0.41	10.6
Model[4,5]		Probability of fixed effects					
Additives		0.560	0.143	0.413	0.004	0.305	0.080
Age		<0.001	0.384	<0.001	0.183	0.363	0.022
BW		<0.001	0.546	<0.001	0.367	0.784	0.125
Additives × Age		0.427	0.492	0.270	0.068	0.501	0.235

ADFI - average daily feed intake; ADG - average daily weight gain; FCR - feed conversion ratio; BW - body weight; SD - standard deviation error; LS-Means - least-square means.
[1] Control - negative control (without additive); PA - phytogenic additives; ATB - antibiotics.
[2] Least-square means of inter experimental groups.
[3] Δ - obtained by the difference between the treatments (intra-experimental) with phytogenic additives or with antibiotics compared to the respective negative control group; values followed by distinct letters differ by Fischer's test (P<0.05), expressed in percentage.
[4] Studies (experiments) entered in the model as a random-effect class variable, and the variables age (average between the initial and final age of each evaluation, expressed in d), BW as average between initial and final body weight of each evaluation, expressed in kg.
[5] Probability at 5%.

The intercepts of the equations implied that ΔADG was 0.96% for phytogenic additives and 3.66% for antibiotics when ΔADFI was zero (Figure 2). Correlating the groups in the equations represented in the graph, we detected a quadratic effect for PA and linear effect for ATB. This denotes that the ADG response increased proportionately with ADFI in both groups. However, this response was predominant in piglets fed diets containing antibiotics. The collective use of phytogenic additives in piglet diets was better than the isolated use of plant-active compounds (Figure 3). Here, the intercepts of the equations indicate that ΔADG was 0.99% for the combined use of diverse compounds from PA and −1.24% for the benefit of only one plant extract when ΔADFI was zero.

4. Discussion

In a meta-analysis, it is imperative to consider the factors that can influence the data population. This study compiled numerous fixed and random factors and included them in the data analysis. However, factors such as diet patterns, ambient temperature, and the concentration of additives incorporated in the diets (Table 1) when integrated could not be estimated owing to the small sample size.

The initial BW and age of piglets are factors that impact feed intake and growth rate, especially in the initial nursery phase. Abrupt changes in dietary patterns, sanitary challenges, and housing can induce a drop in immunity and activation of inflammatory responses, especially in younger animals, due to gastrointestinal immaturity (Lallès et al., 2009). Here, the performance of unchallenged piglets fed diets containing antibiotics was superior to that of piglets fed diets containing phytogenic additives and no additive (negative control). Piglets in antibiotics-based treatment indicate enhancement in performance, which is attributed to controlling the growth of pathogenic bacteria and stimulating the beneficial intestinal bacterial population. Antimicrobials act via intestinal modulation, diminishing the production of growth-depressing metabolites, inhibiting the growth of pathogenic microorganisms, thereby reducing the competition for nutrients, facilitating better absorption by the intestinal epithelium (Helm et al., 2019). In many cases, combinations of different classes, such as macrolides (tiamulin and lincomycin), polymyxins (colistin), and aminoglycosides (bacitracin), are more effective in enhancing piglet performance (Dutra et al., 2021).

Table 3 - Morphometric analysis of small intestine fractions of unchallenged nursery piglets feeding with diets containing phytogenic additives or antibiotics

Additive[1]	n	Villus height (µm)					
		Duodenum		Jejunum		Ileum	
		LS-Means[2]	Δ (%)[3]	LS-Means	Δ (%)	LS-Means	Δ (%)
Control	17	485.3	0.0	407.6	0.0	332.0	0.0
PA	34	483.9	6.2	441.9	8.5	361.0	9.9
ATB	15	475.1	1.8	430.4	5.6	334.0	1.6
SD		23.4	3.7	10.8	11.3	22.2	8.0
Model[4]		Probability of fixed effects					
Additives		0.682	0.340	0.812	0.198	0.261	0.259
Age		0.720	0.875	0.841	0.957	0.754	0.835
BW		0.027	0.665	0.036	0.961	0.581	0.390
Additives × Age		0.384	0.502	0.600	0.931	0.909	0.692
Additives × BW		0.820	0.804	0.516	0.931	0.221	0.319
Additive[1]	n	Crypt depth (µm)					
		Duodenum		Jejunum		Ileum	
		LS-Means	Δ (%)[3]	LS-Means	Δ (%)	LS-Means	Δ (%)
Control	17	188.8	0.0	218.5a	0.0a	200.0	0.0
PA	34	188.2	−1.9	219.0a	1.2a	194.4	−1.7
ATB	15	184.6	0.7	245.9b	12.7b	205.6	1.5
SD		14.0	6.7	23.2	10.4	16.9	7.8
Model[4,5]		Probability of fixed effects					
Additives		0.709	0.490	0.031	0.014	0.201	0.173
Age		0.776	0.744	0.975	0.928	0.868	0.878
BW		0.504	0.383	0.882	0.787	0.677	0.712
Additives × Age		0.991	0.951	0.583	0.330	0.717	0.448
Additives × BW		0.552	0.395	0.766	0.935	0.934	0.967
	Means	Villus height:crypt depth					
		Duodenum		Jejunum		Ileum	
Control	2.00	2.57		1.87		1.66	
PA	2.20	2.57		2.02		1.86	
ATB	1.98	2.57		1.75		1.62	

BW - body weight; SD - standard deviation error; LS-Means - least-square means.
[1] Control - negative control (without additive); PA - phytogenic additives; ATB - antibiotics.
[2] Least-square means of inter experimental groups.
[3] Δ - obtained by the difference between the treatments (intra-experimental) with phytogenic additives or with antibiotics compared to the negative control group; values followed by distinct letters differ by Fischer's test (P<0.05), expressed in percentage.
[4] Age and final body weight of each study.
[5] Probability at 5%.

Although the performance results with the use of antibiotics were superior, it is vital to consider the positive results of the use of phytogenic additives in intestinal morphometry. Phytogenic additives indirectly boost performance by increasing microbial diversity and preventing pathogenic bacteria from triggering inflammatory responses (Xu et al., 2018). This condition favors the growth of villi with a lower cell turnover rate (Wei et al., 2020), and consequently, better utilization of nutrients of the diet due to a lower maintenance requirement (Wang et al., 2020).

Microbial diversity favors villus growth and curtails cell turnover in crypts (Heo et al., 2013). Antibiotic use during the nursery period has been identified to negatively affect gut microbial diversity and resistant bacteria proliferation (Nowland et al., 2019). Conversely, phytogenic additives only inhibit the growth of some bacterial groups (Li et al., 2012). A good indicator of efficiency in nutrient absorption is the villus height:crypt depth (VH:CD) ratio. The higher the ratio, the greater the villus height and lower the crypt depth, the structures responsible for expanding the contact surface for nutrient absorption (Ferreira et al., 2020). In our study, the mean VH:CD values (P<0.05) were 2.20 for herbal extracts, 2.00 for the negative control, and 1.98 for antibiotics.

In the relationship between ADG and ADFI variation (Figures 2 and 3), the ADG response escalated in piglets fed diets with phytogenic additives or antibiotics. However, this response was higher in piglets fed diets containing antibiotics than in those fed diets containing phytogenic additives. The efficacy of antibiotics as growth promoters in piglets is represented by the small dispersion between points and is denoted by the linear effect on weight gain. These results corroborate the findings of Cardinal et al. (2021), who observed, through meta-analysis, an increase in weight gain by 6.5% in nursery piglets, but the incorporation of antibiotics to the diet did not affect feed intake.

In piglets fed phytogenic additives, there was a greater dispersion between the results obtained. This was possibly due to the different active principles studied and mechanisms of action that can enhance weight gain of piglets. In this study, the mix or combination of these active substances of phytogenic additives enriched the weight gain of piglets compared with their isolated use. This response may be associated with the diverse mechanisms of action in combination with phytogenic additives in the diet. Combined phytogenic additives may be more effective than specific antibiotics in nursery piglets (Lallès and Montoya, 2021).

Investigating the impact of phytogenic additives through meta-analysis is challenging owing to intra-study complexity. The diversity of plant extracts (source, form of administration, and level), their isolated or combined use (blends), characteristics inherent to each active principle, and their mechanisms of action facilitate *in vivo* studies on microbial modulation and intestinal health. These help to develop a better understanding of their effects on the performance of nursery piglets. When viewed together, the peculiarities of the production system, including the sanitary challenge, variation in age and weight of piglets at the beginning of the phase, housing, and feeding conditions, must always be considered.

5. Conclusions

Antibiotics enhance the performance of unchallenged nursery pigs, but increased crypt depth in the jejunum. Performance of nursery piglets is superior with use of combined phytogenic additives compared to the isolated use of plant extracts.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization: Matoso, L. G. and Primieri, C. C. **Data curation:** Primieri, C. C. **Formal analysis:** Andrade, E. and Lehnen, C. R. **Investigation:** Matoso, L. G. and Primieri, C. C. **Methodology:** Lehnen, C. R. **Project administration:** Matoso, L. G.; Primieri, C. C. and Lehnen, C. R. **Supervision:** Weege, V.; Mass, A. P. H. and Lehnen, C. R. **Visualization:** Andrade, E. and Lehnen, C. R. **Writing – original draft:** Primieri, C. C. **Writing – review & editing:** Matoso, L. G.; Weege, V.; Mass, A. P. H. and Lehnen, C. R.

Acknowledgments

We acknowledge the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), the Fundação Araucária, and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grant 455991/2014-6) for grants awarded; and CNPq for the financial support (grant 455991/2014-6).

References

Barroca, C. C. 2011. Aditivos em dietas para leitões de 21 a 49 dias de idade. Dissertação (M.Sc.). Universidade Federal de Viçosa, Viçosa, MG.

Branco, P. A. C.; Soares, R.; Vieites, F.; Cabral, N. and Tavares, E. 2011. Efeito de óleos essenciais como promotores de crescimento em leitões recém-desmamado. Archivos de Zootecnia 60:699-706. https://doi.org/10.4321/S0004-05922011000300057

Caldara, F. R.; Rosa, P. S. G.; Reis, N. M. O.; Garcia, R. G.; Paz, I. C. L. A.; Almeida, F. A. and Ferreira, V. M. O. S. 2009. Alho e orégano como substitutos de antimicrobianos na alimentação de leitões desmamados. Agrarian 2:143-152.

Camilleri, M.; Madsen, K.; Spiller, R.; Van Meerveld, B. G. and Verne, G. N. 2012. Intestinal barrier function in health and gastrointestinal disease. Neurogastroenterology & Motility 24:503-512. https://doi.org/10.1111/j.1365-2982.2012.01921.x

Campbell, J. M.; Crenshaw, J. D. and Polo, J. 2013. The biological stress of early weaned piglets. Journal of Animal Science and Biotechnology 4:19. https://doi.org/10.1186/2049-1891-4-19

Cardinal, K. M.; Andretta, I.; Silva, M. K.; Stefanello, T. B.; Schroeder, B. and Ribeiro, A. M. L. 2021. Estimation of productive losses caused by withdrawal of antibiotic growth promoter from pig diets – Meta-analysis. Scientia Agricola 78:e20200266. https://doi.org/10.1590/1678-992X-2020-0266

Colina, J. J.; Lewis, A. J.; Miller, P. S. and Fischer, R. L. 2001. Dietary manipulation to reduce aerial ammonia concentrations in nursery pig facilities. Journal of Animal Science 79:3096-3103. https://doi.org/10.2527/2001.79123096x

Costa, L. B.; Berenchtein, B.; Almeida, V. V.; Tse, M. L. P.; Braz, D. B.; Andrade, C.; Mourão, G. B. and Miyada, V. S. 2011. Aditivos fitogênicos e butirato de sódio como promotores de crescimento de leitões desmamados. Archivos de Zootecnia 60:687-698. https://doi.org/10.4321/S0004-05922011000300056

Costa, L. B.; Tse, M. L. P. and Miyada, V. S. 2007. Extratos vegetais como alternativas aos antimicrobianos promotores de crescimento para leitões recém-desmamados. Revista Brasileira de Zootecnia 36:589-595. https://doi.org/10.1590/S1516-35982007000300011

Cho, J. H.; Zhang, S. and Kim, I. H. 2012. Effects of anti-diarrhoeal herbs on growth performance, nutrient digestibility, and meat quality in pigs. Asian-Australasian Journal of Animal Sciences 25:1595-1604. https://doi.org/10.5713/ajas.2012.12339

Clouard, C. and Val-Laillet, D. 2014. Impact of sensory feed additives on feed intake, feed preferences, and growth of female piglets during the early postweaning period. Journal of Animal Science 92:2133-2140. https://doi.org/10.2527/jas.2013-6809

Ding, Y. Y.; Zhang, C. H.; He, X. L.; Huang, L. and Yin, J. 2011. Growth performance responses and indicators of gastrointestinal health in early weaned pigs fed Chinese herbal medicine additives-supplements diets. Journal of Animal and Veterinary Advances 10:1580-1587.

Dutra, M. C.; Moreno, L. Z.; Dias, R. A. and Moreno, A. M. 2021. Antimicrobial use in Brazilian swine herds: Assessment of use and reduction examples. Microorganisms 9:881. https://doi.org/10.3390/microorganisms9040881

Fang, J.; Yan, F. Y.; Kong, X. F.; Ruan, Z.; Liu, Z. Q.; Huang, R. L.; Li, T. J.; Geng, M. M.; Yang, F.; Zhang, Y. Z.; Li, P.; Gong, J.; Wu, G. Y.; Fan, M. Z.; Liu, Y. L.; Hou, Y. Q. and Yin, Y. L. 2009. Dietary supplementation with *Acanthopanax senticosus* extract enhances gut health in weaning piglets. Livestock Science 123:268-275. https://doi.org/10.1016/j.livsci.2008.11.020

Ferreira, J. L.; Watanabe, P. H.; Mendonça, I. B.; Nogueira, B. D.; Ferreira, A. C. S.; Nepomuceno, R. C.; Pascoal, L. A. F.; Almeida, J. M. S.; Guerra, R. R.; Trevisan, M. T. S.; Silva, I. N. G. and Freitas, E. R. 2020. Calcium anacardate and citric acid as growth promoters for weaned piglets. Livestock Science 238:104084. https://doi.org/10.1016/j.livsci.2020.104084

Gazola, A. P.; Carvalho, P. L. O.; Chambo, P. C. S.; Oliveira, A. C. and Genova, J. L. 2016. Utilização do extrato de resíduo da própolis na alimentação de leitões (6 a 8 kg). In: Anais do 2º Encontro Anual de Iniciação Científica, Tecnológica e Inovação, Cascavel.

Gräber, T.; Kluge, H.; Granica, S.; Horn, G.; Brandsch, C. and Stang, G. I. 2014. Studies on the health impact of *Agrimonia procera* in piglets. BMC Veterinary Research 10:210. https://doi.org/10.1186/s12917-014-0210-y

Gois, F. D. 2014. Óleo essencial da aroeira (*Schinus terebinthifolius* Raddi) como alternativa aos antimicrobianos melhoradores de desempenho para leitões recém-desmamados. Dissertação (M.Sc.). Universidade Federal da Bahia, Ilhéus.

Halas, V.; Nochta, I.; Pásti, Z.; Szabó, C.; Tóthi, R.; Tossenberger, J. and Babinszky, L. 2011. Cellular immune response of weaned pigs fed diet supplemented with an essential oil. Agriculturae Conspectus Scientificus 76:279-282.

Hanczakowska, E. and Swiatkiewicz, M. 2012. Effect of herbal extracts on piglet performance and small intestinal epithelial villi. Czech Journal of Animal Science 57:420-429. https://doi.org/10.17221/6316-cjas

Helm, E. T.; Curry, S.; Trachsel, J. M.; Schroyen, M. and Gabler, N. K. 2019. Evaluating nursery pig responses to in-feed sub-therapeutic antibiotics. PLoS ONE 14:e0216070. https://doi.org/10.1371/journal.pone.0216070

Henn, J. D.; Bertol, T. M.; Moura, N. F.; Coldebella, A.; Brum, P. A. R. and Casagrande, M. 2010. Oregano essential oil as food additive for piglets: antimicrobial and antioxidant potential. Revista Brasileira de Zootecnia 39:1761-1767. https://doi.org/10.1590/S1516-35982010000800019

Heo, J. M.; Opapeju, F. O.; Pluske, J. R.; Kim, J. C.; Hampson, D. J. and Nyachoti, C. M. 2013. Gastrointestinal health and function in weaned pigs: a review of feeding strategies to control post-weaning diarrhoea without using in-feed antimicrobial compounds. Journal of Animal Physiology and Animal Nutrition 97:207-237. https://doi.org/10.1111/J.1439-0396.2012.01284.X

Ikeda, N. Y. 2015. Utilização de própolis e probiótico em dietas para leitões recém-desmamados. Dissertação (M.Sc.). Escola Superior de Agricultura "Luiz de Queiroz", Universidade de São Paulo, Piracicaba.

Kipper, M.; Andretta, I.; Quadros, V. R.; Schroeder, B.; Pires, P. G. S.; Franceschina, C. S.; Hickmann, F. M. W. and França, I. 2020. Performance responses of broilers and pigs fed diets with β-mannanase. Revista Brasileira de Zootecnia 49:e20180177. https://doi.org/10.37496/rbz4920180177

Kumar, H.; Chen, B. H.; Kuca, K.; Nepovimova, E.; Kaushal, A.; Nagraik, R.; Bhatia, S. K.; Dhanjal, D. S.; Kumar, V.; Kumar, A.; Upadhyay, N. K.; Verma, R. and Kumar, D. 2020. Understanding of colistin usage in food animals and available detection techniques: A Review. Animals 10:1892. https://doi.org/10.3390/ani10101892

Lallès, J. P.; Bosi, P.; Janczyk, P.; Koopmans, S. J. and Torrallardona, D. 2009. Impact of bioactive substances on the gastrointestinal tract and performance of weaned piglets: a review. Animal 3:1625-1643. https://doi.org/10.1017/S175173110900398X

Lallès, J. P. and Montoya, C. A. 2021. Dietary alternatives to in-feed antibiotics, gut barrier function and inflammation in piglets post-weaning: Where are we now? Animal Feed Science and Technology 274:114836. https://doi.org/10.1016/j.anifeedsci.2021.114836

Lehnen, C. R.; Lovatto, P. A.; Andretta, I.; Rossi, C. A.; Hauschild, L.; Cavazini, N. C. and Fraga, B. N. 2012. Alimentação de leitões em creche com dietas contendo ácido ascórbico e bioflavonóides. Archivos de Zootecnia 61:103-109. https://doi.org/10.4321/S0004-05922012000100011

Lekagul, A.; Tangcharoensathien, V. and Yeung, S. 2019. Patterns of antibiotic use in global pig production: A systematic review. Veterinary and Animal Science 7:100058. https://doi.org/10.1016/J.VAS.2019.100058

Li, S. Y.; Ru, Y. J.; Liu, M.; Xu, B.; Péron, A. and Shi, X. G. 2012. The effect of essential oils on performance, immunity and gut microbial population in weaner pigs. Livestock Science 145:119-123. https://doi.org/10.1016/j.livsci.2012.01.005

Liu, Y.; Song, M.; Che, T. M.; Almeida, J. A. S.; Lee, J. J.; Bravo, D.; Maddox, C. W. and Pettigrew, J. E. 2013. Dietary plant extracts alleviate diarrhea and alter immune responses of weaned pigs experimentally infected with a pathogenic *Escherichia coli*. Journal of Animal Science 91:5294-5306. https://doi.org/10.2527/jas.2012-6194

Long, S. F.; Xu, Y. T.; Pan, L.; Wang, Q. Q.; Wang, C. L.; Wu, J. Y.; Wu, Y. Y.; Han, Y. M.; Yun, C. H. and Piao, X. S. 2018. Mixed organic acids as antibiotic substitutes improve performance, serum immunity, intestinal morphology and microbiota for weaned piglets. Animal Feed Science and Technology 235:23-32. https://doi.org/10.1016/j.anifeedsci.2017.08.018

Lovatto, P. A.; Lehnen, C. R.; Andretta, I.; Carvalho, A. D. and Hauschild, L. 2007. Meta-análise em pesquisas científicas: enfoque em metodologias. Revista Brasileira de Zootecnia 36(suplemento especial):285-294. https://doi.org/10.1590/s1516-35982007001000026

Lovatto, P. A.; Oliveira, V.; Hauptli, L.; Hauschild, L. and Cazarré, M. M. 2005. Alimentação de leitões na creche com dietas sem aditivos antimicrobianos, com alho (*Allium sativum*, L.) ou colistina. Ciência Rural 35:656-659. https://doi.org/10.1590/S0103-84782005000300027

Maenner, K.; Vahjen, W. and Simon, O. 2011. Studies on the effects of essential-oil-based feed additives on performance, ileal nutrient digestibility, and selected bacterial groups in the gastrointestinal tract of piglets. Journal of Animal Science 89:2106-2112. https://doi.org/10.2527/jas.2010-2950

Manzanilla, E. G.; Nofrarías, M.; Anguita, M.; Castillo, M.; Perez, J. F.; Martín-Orúe, S. M.; Kamel, C. and Gasa, J. 2006. Effects of butyrate, avilamycin, and a plant extract combination on the intestinal equilibrium of early-weaned pigs. Journal of Animal Science 84:2743-2751. https://doi.org/10.2527/jas.2005-509

Michiels, J.; Missotten, J.; Van Hoorick, A.; Ovyn, A.; Fremaut, D.; De Smet, S. and Dierick, N. 2010. Effects of dose and formulation of carvacrol and thymol on bacteria and some functional traits of the gut in piglets after weaning. Archives of Animal Nutrition 64:136-154. https://doi.org/10.1080/17450390903499915

Mueller, K.; Blum, N. M.; Kluge, H.; Bauerfeind, R.; Froehlich, J.; Mader, A.; Wendler, K. R. and Mueller, A. S. 2012. Effects of broccoli extract and various essential oils on intestinal and faecal microflora and on xenobiotic enzymes and the antioxidant system of piglets. Open Journal of Animal Sciences 2:78-98. https://doi.org/10.4236/ojas.2012.22012

Namkung, H.; Li, M.; Gong, J.; Yu, H.; Cottrill, M. and de Lange, C. F. M. 2004. Impact of feeding blends of organic acids and herbal extracts on growth performance, gut microbiota and digestive function in newly weaned pigs Canadian Journal of Animal Science 84:697-704. https://doi.org/10.4141/A04-005

Neill, C. R.; Nelssen, J. L.; Tokach, M. D.; Goodband, R. D.; DeRouchey, J. M.; Dritz, S. S.; Groesbeck, C. N. and Brown, K. R. 2006. Effects of oregano oil on growth performance of nursery pigs. Journal of Swine Health and Production 14:312-316.

Nowland, T. L.; Plush, K. J.; Barton, M. and Kirkwood, R. N. 2019. Development and function of the intestinal microbiome and potential implications for pig production. Animals 9:76. https://doi.org/10.3390/ani9030076

Oetting, L. L.; Utiyama, C. E.; Giani, P. A.; Ruiz, U. S. and Miyada, V. S. 2006. Efeitos de extratos vegetais e antimicrobianos sobre a digestibilidade aparente, o desempenho, a morfometria dos órgãos e a histologia intestinal de leitões recém-desmamados. Revista Brasileira de Zootecnia 35:1389-1397. https://doi.org/10.1590/S1516-35982006000500019

Oliveira, M. F. 2015. Índices produtivos de leitões em fase de creche alimentados com dietas contendo bioflavonóides e ácido ascórbico (extratos vegetais). Dissertação (M.Sc.). Universidade Federal de Santa Maria, Santa Maria.

Omonijo, F. A.; Ni, L.; Gong, J.; Wang, Q.; Lahaye, L. and Yang, C. 2018. Essential oils as alternatives to antibiotics in swine production. Animal Nutrition 4:126-136. https://doi.org/10.1016/j.aninu.2017.09.001

Ortiz-Rueda, D. M.; Ruiz-Salazar, J. A. and Pereira-Tupaz, R. L. 2012. Efecto del acido cítrico sobre los parámetros productivos, metabólicos y coliformes totales en lechones durante las cuatro primeras semanas postdestete. Revista Investigación Pecuaria 1:32-40.

Pastorelli, H.; van Milgen, J.; Lovatto, P. and Montagne, L. 2012. Meta-analysis of feed intake and growth responses of growing pigs after a sanitary challenge. Animal 6:952-961. https://doi.org/10.1017/S175173111100228X

Pedroso, A. A.; Oetting, L. L.; Utiyama, C. E.; Menten, J. F. M.; Lambais, M. R. and Miyada, V. S. 2005. Variabilidade espacial da comunidade bacteriana intestinal de suínos suplementados com antibióticos ou extratos herbais. Revista Brasileira de Zootecnia 34:1225-1233. https://doi.org/10.1590/S1516-35982005000400018

Rahman, M. R. T.; Fliss, I. and Biron, E. 2022. Insights in the development and uses of alternatives to antibiotic growth promoters in poultry and swine production. Antibiotics 11:766. https://doi.org/10.3390/antibiotics11060766

Ramos, R. C.; Bolzan, R. P.; Pirovani, C. H. D.; Oliveira, A. F. M. and Porfirio, L. C. 2013. *Chenopodium ambrosioides* L. como promotor de crescimento em suínos na fase de creche. Enciclopédia Biosfera 9:3757-3764.

Remus, A.; Hauschild, L.; Andretta, I.; Kipper, M.; Lehnen, C. R. and Sakomura, N. K. 2014. A meta-analysis of the feed intake and growth performance of broiler chickens challenged by bacteria. Poultry Science 93:1149-1158. https://doi.org/10.3382/ps.2013-03540

Santana, M. B.; Melo, A. D. B.; Cruz, D. R.; Garbossa, C. A. P.; Andrade, C.; Cantarelli, V. S. and Costa, L. B. 2015. Alternatives to antibiotic growth promoters for weanling pigs. Ciência Rural 45:1093-1098. https://doi.org/10.1590/0103-8478cr20140407

Santos, C. M. R. 2010. Efeito da utilização de óleos essenciais e ácidos orgânicos microencapsulados na alimentação do leitão: crescimento, digestibilidade, fisiologia digestiva. Dissertação (M.Sc.). Instituto Superior de Agronomia, Universidade Técnica de Lisboa, Lisboa.

Sauvant, D.; Letourneau-Montminy, M. P.; Schmidely, P.; Boval, M.; Loncke, C. and Daniel, J. B. 2020. Review: Use and misuse of meta-analysis in Animal Science. Animal 14:s207-s222. https://doi.org/10.1017/S1751731120001688

Sauvant, D.; Schmidely, P. and Daudin, J. J. 2005. Les méta-analyses des données expérimentales: Applications en nutrition animale. INRA Productions Animales 18:63-73. https://doi.org/10.20870/productions-animales.2005.18.1.3510

Silva Júnior, C. D. 2016. Aditivo alternativo, associado ou não ao antimicrobiano, na dieta de leitões recém-desmamados. Dissertação (M.Sc.). Universidade Estadual Paulista, Dracena.

Suzuki, O. H.; Flemming, J. S. and Silva, M. E. T. 2008. Uso de óleos essenciais na alimentação de leitões. Revista Acadêmica Ciência Animal 6:519-526.

Toseti, L. B.; Rodrigues, D. C.; Rubio, M. S.; Melo, V. F. P.; Deus, A. S. N. and Filardi, R. S. 2013. Incidência parasitológica em leitões desmamados suplementados com própolis e pimenta de java. In: 7º Encontro de Ciências da Vida, Universidade Estadual Paulista "Júlio de Mesquita Filho", Ilha Solteira.

Utiyama, C. E.; Oetting, L. L.; Giani, P. A.; Ruiz, U. S. and Miyada, V. S. 2006. Efeitos de antimicrobianos, prebióticos, probióticos e extratos vegetais sobre a microbiota intestinal, a freqüência de diarréia e o desempenho de leitões recém-desmamados. Revista Brasileira de Zootecnia 35:2359-2367. https://doi.org/10.1590/S1516-35982006000800023

Václavková, E. and Bečková, R. 2008. Effect of herbal extract on growth parameters of weaned piglets. Research in Pig Breeding 2:36-38.

Vale, P. A. C. B.; Soares, R. T. R. N.; Brêtas, A. A.; Cabral, N. O.; Vieites, F. M.; Bonaparte, T. P. and Mota, T. 2010. Óleos essenciais em dietas para leitões recém-desmamados. Global Science and Technology 3:75-83.

Wang, D.; Zhou, L.; Zhou, H.; Hu, H. and Hou, G. 2021. Chemical composition and protective effect of guava (*Psidium guajava* L.) leaf extract on piglet intestines. Journal of the Science of Food and Agriculture 101:2767-2778. https://doi.org/10.1002/jsfa.10904

Wang, M.; Huang, H.; Hu, Y.; Liu, Y.; Zeng, X.; Zhuang, Y.; Yang, H.; Wang, L.; Chen, S.; Yin, L.; He, S.; Zhang, S.; Li, X. and He, S. 2020. Effects of dietary supplementation with herbal extract mixture on growth performance, organ weight and intestinal morphology in weaning piglets. Journal of Animal Physiology and Animal Nutrition 104:1462-1470. https://doi.org/10.1111/jpn.13422

Wei, H. K.; Wang, J.; Cheng, C.; Jin, L. Z. and Peng, J. 2020. Application of plant essential oils in pig diets. p.227-237. In: Feed additives: Aromatic plants and herbs in animal nutrition and health. Florou-Paneri, P.; Christaki, E. and Giannenas, I., eds. Academic Press. https://doi.org/10.1016/B978-0-12-814700-9.00013-3

Xu, Y. T.; Liu, L.; Long, S. F.; Pan, L. and Piao, X. S. 2018. Effect of organic acids and essential oils on performance, intestinal health and digestive enzyme activities of weaned pigs. Animal Feed Science and Technology 235:110-119. https://doi.org/10.1016/j.anifeedsci.2017.10.012

Yan, L.; Meng, Q. W. and Kim, I. H. 2012. Effect of an herb extract mixture on growth performance, nutrient digestibility, blood characteristics, and fecal microbial shedding in weanling pigs. Livestock Science 145:189-195. https://doi.org/10.1016/j.livsci.2012.02.001

Zangeronimo, M. G.; Cantarelli, V. S.; Fialho, E. T.; Amaral, N. O.; Silveira, H.; Pereira, L. M. and Pereira, L. J. 2011. Herbal extracts and symbiotic mixture replacing antibiotics in piglets at the initial phase. Revista Brasileira de Zootecnia 40:1045-1051. https://doi.org/10.1590/S1516-35982011000500016

Zhai, H.; Liu, H.; Wang, S.; Wu, J. and Kluenter, A. M. 2018. Potential of essential oils for poultry and pigs. Animal Nutrition 4:179-186. https://doi.org/10.1016/j.aninu.2018.01.005