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Efficacy of Nano-Phytobiotics to Improve Growth Performance of Broiler Chickens: Evidence from a Meta-Analysis

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ABSTRACT

The ban of antibiotic growth promoters in many countries necessitate the need for alternatives. This study aimed to assess the growth-promoting potency of nano-phytobiotics (NP) on broiler chickens by using a meta-analysis approach. A systematic search was conducted using online databases. Data of average daily feed intake (ADFI), average daily gain (ADG), and feed conversion ratio (FCR) were pooled using a random-effect model and the overall effect size was quantified using mean difference (MD). Heterogeneity among the studies was checked using I^2 statistics. A total of 11 studies (31 comparisons) using 3,584 broiler chickens were involved in this meta-analysis. Inclusion of NP had no significant effect on ADFI (MD=-1.20 g/bird/d; P=0.157; I^2=32%). However, NP significantly improved ADG (MD=2.16 g/bird/d; P=0.002; I^2=90%) and FCR (MD=-0.09; P<0.001; I2=91%). Subgroup analysis revealed that NP significantly improved (P<0.05) ADG when the studies using dose of 45-200 and 1,000-10,000 ppm, as well as 42 d study period. Meta-regression analysis also indicated that ADG improvement significantly associated (P<0.05) with the NP dose and study duration, which could explain 21% and 20% of heterogeneity, respectively. This meta-analysis provides evidence that NP inclusion could improve ADG and FCR without alter ADFI on broiler chickens. However, their efficacy may vary according to the NP dose and study duration.

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Introduction

The indiscriminate use of antibiotics growth promoters (AGP) leads to the incorporation of drug residue in animal products and invasion of resistant microbial that threatens food safety and human health (Davis *et al*., 2018; Roth *et al*., 2019; Yang *et al*., 2019; Younessi *et al*., 2020; Haque *et al*., 2021). Realizes that hazard situation, many countries are then voluntarily phase out AGP from animal production (Bacanlı and Başaran, 2019; Coyne *et al*., 2019). Consequently, the search for suitable alternatives to AGP is highly demanded.

One of the potential AGP alternatives is plant-derived bioactive compounds, which is commonly termed as phytobiotics. A body of knowledge indicated that phytobiotics had antimicrobial and antioxidant actions (Yashin *et al*., 2017; Anand *et al*., 2019; Reyes-Jurado *et al*., 2020; Valdivieso-Ugarte *et al*., 2019), which may support animal productivity and products quality (Andri *et al*., 2016; Andri *et al*., 2018; Edi *et al*., 2018; Gheisar and Kim, 2018; Kothari *et al*., 2019; Pliego *et al*., 2020; Deminicis *et al*., 2021). However, the use of phytobiotics is still encounter some limitation such as low chemical stability and poor water solubility (Prakash *et al*., 2018; Das *et al*., 2019; Park *et al*., 2019; Sharifi *et al*., 2020).

The use of nanotechnology is recently proposed as a gold standard for the preparation of phytobiotics. Nanotechnology could provide protection against various harsh condition as well as enhancement of solubility and bioactivity (Fan *et al*., 2017; Ong *et al*., 2017; Lee *et al*., 2019; Shetta *et al*., 2019; Osama *et al*., 2020; Salehi *et al*., 2020). Moreover, the inclusion of nano-phytobiotics (NP) in broiler chickens di*et al*so reported to have higher growth promoting effects as compared to the free-phytobiotics (Nouri, 2019; Ibrahim *et al*., 2021; Amiri *et al*., 2021).

Meta-analysis is a valuable statistical tool to evaluate the efficacy of certain intervention (Cipriani *et al*., 2013). Through meta-analysis, data from multiple independent studies were integrated so that it could resolve seemingly contradictory results (Gurevitch *et al*., 2018) and ultimately could provide more robust evidence. This study was carried out to evaluate the effects of NP inclusion on the average daily feed intake (ADFI), average daily gain (ADG), and feed conversion ratio (FCR) of broiler chickens by using a meta-analysis approach.

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Materials and methods

Study search and selection

This meta-analysis adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page *et al*., 2021). A systematic search was conducted using three online databases (Scopus, PubMed, and Google Scholar). The keywords used were "nano" AND "growth OR performance" AND "broiler OR chick". The last search was performed on May 2, 2021. The studies were included in this meta-analysis when met the following criteria: 1) using broiler chickens, 2) using NP intervention, 3) have control group (without any feed additives or AGP), 4) reporting ADFI, ADG, and FCR, and 5) using randomized design.

The phase of study search and selection process is presented on PRISMA flow diagram (Figure 1). A total of 125 records were identified from database searching. Twenty nine records were removed before screening due to the duplication. Evaluation on the title and abstract resulting in the removal of 80 studies due to the irrelevance issue. One report was also removed because the full text not accessible. Four reports were further removed because ineligible data and study design. Finally, only 11 studies met the inclusion criteria and used in this meta-analysis.

The following information were extracted from each of the included studies: 1) author name and publication year, 2) number of NP treatments, 3) number of birds per treatment, 4) birds strain, 5) birds sex, 6) NP type, 7) NP dose, and 8) study duration. Moreover, number of replicates, mean values, and variation measures (standard deviation, standard error, or standard error of mean) of ADFI, ADG, and FCR were also included in the database. When the studies presenting standard error or standard error of mean, it was converted into the standard deviation (Greig *et al*., 2012; Andri *et al*., 2020a). In the case of more than one NP dose or NP type used in a study, each treatment was compared with control individually.

Meta-analysis procedure

Meta-analysis was performed using R version 4.0.5 (R Core Team, 2021) equipped with 'meta' package version 4.18-0 (Balduzzi *et al*., 2019), 'metafor' package version 2.4-0 (Viechtbauer, 2010), and 'dmetar' package (Harrer *et al*., 2019). The effect size was quantified as a mean difference (MD). The overall effect was pooled using a random-effect model with Hartung-Knapp-Sidik-Jonkman adjustment (Harrer *et al*., 2021). A statistical significance was declared when the overall effect had $P<0.05$. Heterogeneity was checked using I^2 statistic, with $I^2>50\%$ was considered as an existence of substantial heterogeneity among the studies. Forest plot was constructed to visualize the effect of NP inclusion on ADFI, ADG, and FCR. The effect size of each study was showed in a point with its 95% confidence interval (CI). The weighted contribution of each study also showed in the forest plot. The overall effect size was figured out with diamond shape below the included studies.

Subgroup and meta-regression analysis were used to further explore the source of heterogeneity. Subgroup analysis was specified with categorical data, namely NP dose (45-200 ppm, 360-800, and 1,000-10,000 ppm), and study duration (28-35 d and 42 d). In addition, meta-regression was conducted with continuous data (NP dose and study duration). To test the robustness of meta-analysis result, sensitivity analysis was performed by using a leave-one-out method (Harrer *et al*., 2021).

Results

Study characteristics

The included studies were published between 2014 and 2021. There were 31 comparisons derived from the included studies (Table 1). The number of broiler chickens involved in

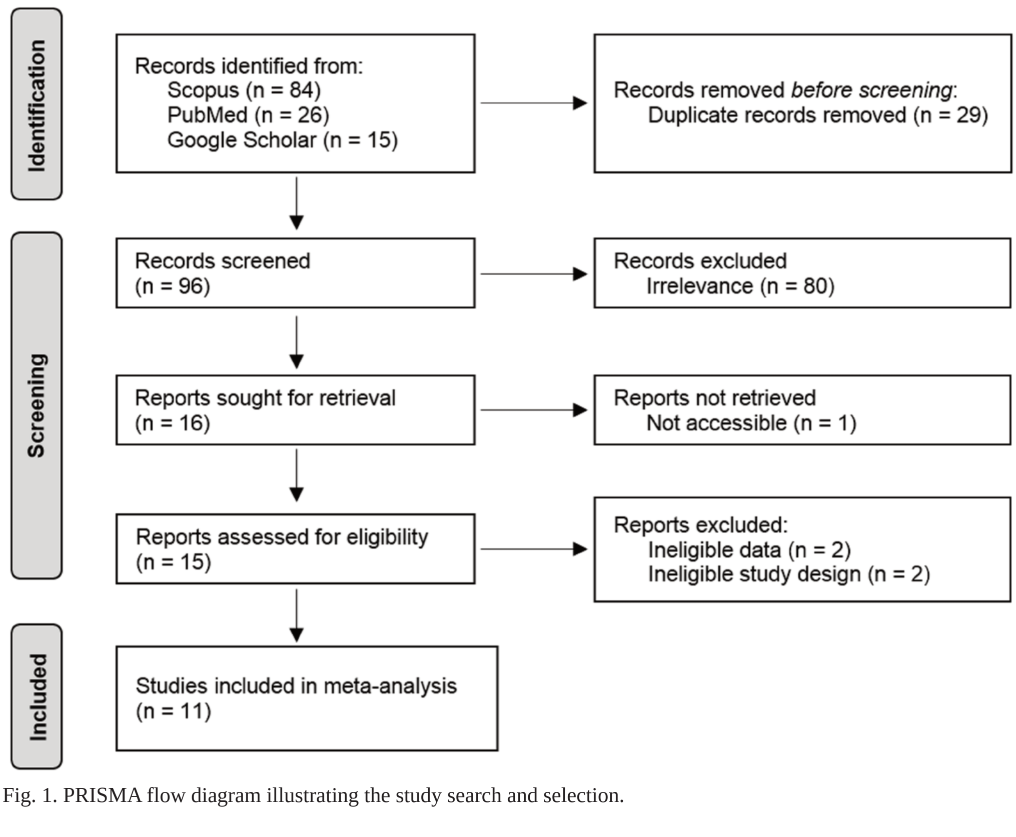

Fig. 1. PRISMA flow diagram illustrating the study search and selection.

this meta-analysis were 3,584 birds. Ross was the most frequent strain in the included studies (64%), followed by Lohmann (27%) and Cobb (9%). About 45% of the included studies using both male and female chicken, while another 36% studies using male chicken. Two studies (18%) did not provide details about sex of the birds. Plant extracts were used to develop nano-phytobiotics in the 45% of the included studies, while plant essential oils used in another 36% studies. About 18% of the included studies using nano-phytobiotics with purified bioactive compounds. The dose of nano-phytobiotics inclusion ranged widely from 0 to 10,000 ppm. Nano-phytobiotics treatment ranged from 28 to 42 days.

Primary analysis

Figure 2 shows that nano-phytobiotics inclusion had no significant effect (P>0.05) on ADFI, with no substantial heterogeneity among the studies (I^2<50%). On the other hand, nano-phytobiotics intervention significantly improved (P<0.05) ADG (Figure 3) and FCR (Figure 4). However, heterogeneity among the studies of ADG and FCR was substantial, as indicated by I^2>50%.

Subgroup analysis

As can be seen on Table 2, nano-phytobiotics significantly improved (P<0.05) ADG when the studies using dose of 45-200 and 1,000-10,000 ppm, as well as 42 d study period. Nano-phytobiotics dose at 45-200 and 360-800 ppm significantly improved (P<0.05) FCR. Whereas 1,000-10,000 ppm nano-phytobiotics had no significant effect (P>0.05) on FCR. Both study duration (28-35 d and 42 d) significantly improved (P<0.05) FCR.

Meta-regression analysis

Table 3 indicates that ADG improvement had significant association (P<0.05) with nano-phytobiotics dose and study duration. These covariates could explain about 21% and 20% of heterogeneity, respectively. However, FCR improvement was

Table 1. Main characteristics of the included studies.

Author	n[1]	n birds[2]	Strain	Sex	Nano-phytobiotics type	Dose (ppm)	Duration (d)
Amiri *et al*. (2021)	2	150	Ross	Male	Nano-garlic EO[3]	0, 100, 200	42
Hidayat *et al*. (2021)	4	60	Lohmann	Both	Nano-guava leaf extract	0, 45, 90, 135, 180	33
Ibrahim *et al*. (2021)	3	300	Ross	Male	Nano-thymol	0, 2,500, 5,000, 10,000	42
Amiri *et al*. (2020)	2	150	Ross	Male	Nano-cumin EO	0, 100, 200	42
Baskara *et al*. (2020)	3	40	Lohmann	Both	Nano-cinnamon EO	0, 200, 400, 800	28
El-Gogary *et al*. (2019)	2	28	Cobb	Both	Nano-garlic extract	0, 500, 1,000	42
Nouri (2019)	3	75	Ross	Both	Nano-mint EO, nano-thyme EO, nano-cinnamon EO	0, 440, 440, 440	42
Barbarestani *et al*. (2017)	1	80	Ross	Both	Nano-peppermint extract	0, 200	42
Meimandipour *et al*. (2017)	3	30	Ross	NA[3]	Nano-*Aloe vera* extract, nano-dill extract, nano-nettle root extract	0, 360, 360, 360	42
Rahmani *et al*. (2017)	4	50	Ross	Male	Nano-curcumin	0, 200, 400, 200, 400	42
Sundari *et al*. (2014)	4	12	Lohmann	NA	Nano-turmeric extract	0, 2,000, 4,000, 6,000, 8,000	35

[1]Number of comparison, [2]Number of birds per treatment, [3]Essential oil, [4]Not available

Table 2. Subgroup analysis of the effect of nano-phytobiotics inclusion on growth performance of broiler chickens

Variable	Subgroup	n	MD	95% CI	*p*	I^2	*p* subgroup
ADG	Dose (ppm)						0.317
	45-200	12	1.42	[0.16; 2.69]	0.028	23%	
	360-800	11	0.89	[-0.90; 2.67]	0.329	0%	
	1,000-10,000	8	3.79	[0.48; 7.10]	0.025	95%	
	Duration (d)						< 0.001
	28-35	11	-0.1	[-1.23; 1.04]	0.865	0%	
	42	20	3.38	[1.73; 5.04]	< 0.001	92%	
FCR	Dose (ppm)						0.051
	45-200	12	-0.1	[-0.13; -0.07]	< 0.001	0%	
	360-800	11	-0.05	[-0.08; -0.03]	< 0.001	0%	
	1,000-10,000	8	-0.08	[-0.16; 0.01]	0.068	97%	
	Duration (d)						0.158
	28-35	11	-0.06	[-0.10; -0.03]	< 0.001	1%	
	42	20	-0.1	[-0.14; -0.07]	< 0.001	93%	

ADG: Average daily gain; FCR: Feed conversion ratio

Table 3. Meta-regression of the effect of nano-phytobiotics inclusion on growth performance of broiler chickens

Variable	Covariate	n	Coefficient	95% CI	*p*	R^2
ADG	Dose (ppm)	31	0.0007	[0.0003; 0.0012]	0.001	21%
	Duration (d)	31	0.3328	[0.0976; 0.5680]	0.007	20%
FCR	Dose (ppm)	31	0	[-0.0000; 0.0000]	0.15	0%
	Duration (d)	31	-0.0022	[-0.0072; 0.0029]	0.388	0%

ADG: Average daily gain; FCR: Feed conversion ratio

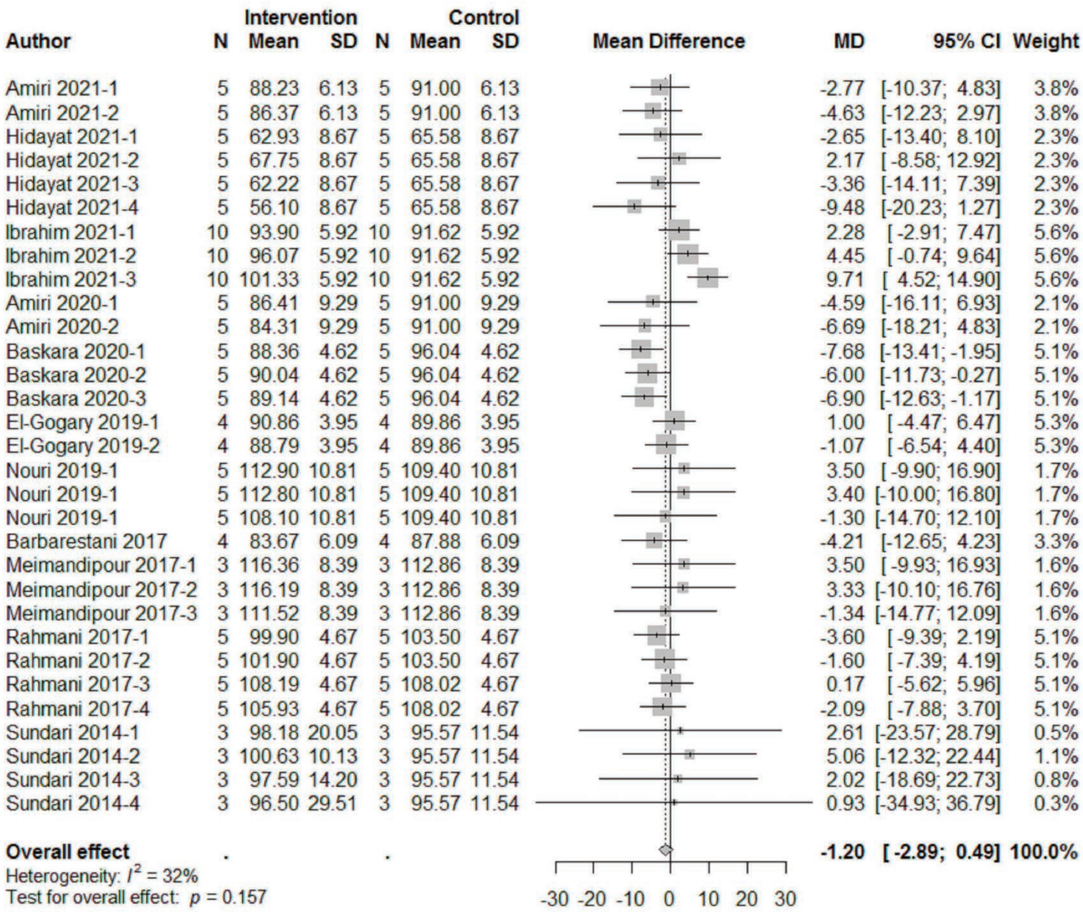

Fig. 2. Forest plot of the effect of nano-phytobiotics inclusion on ADFI of broiler chickens.

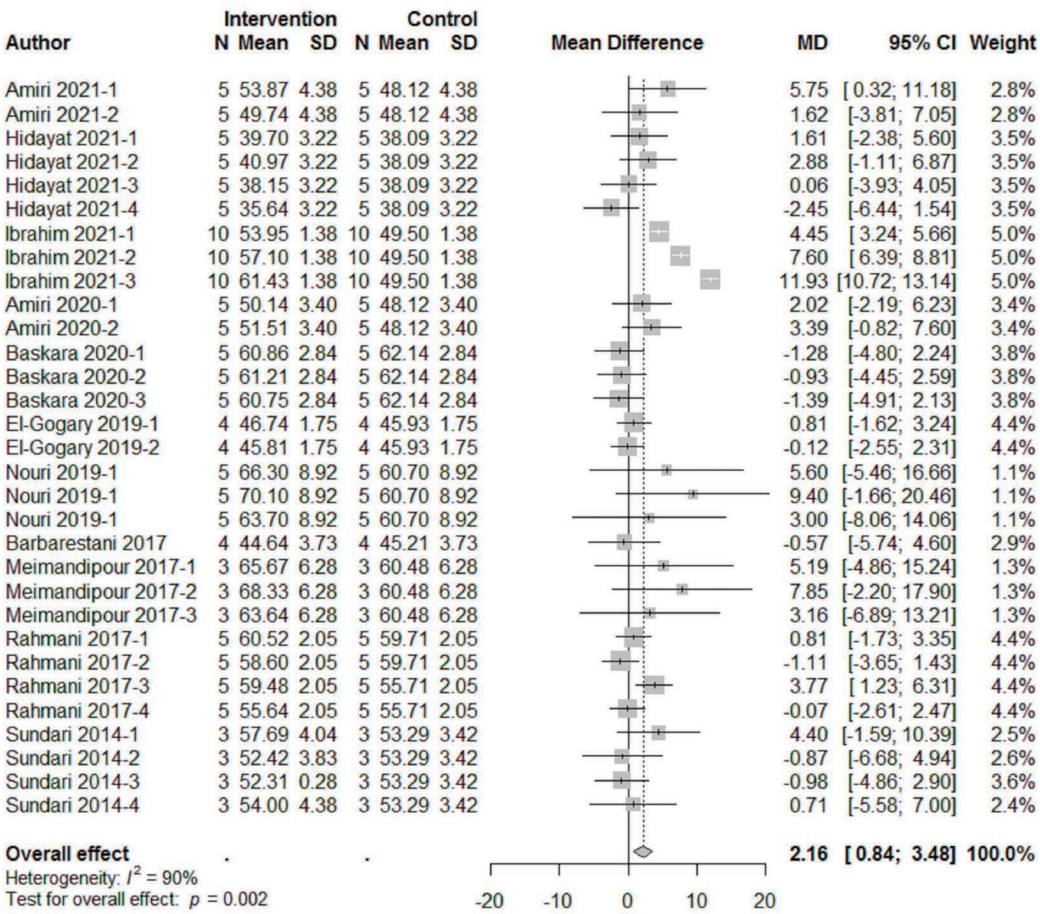

Fig. 3. Forest plot of the effect of nano-phytobiotics inclusion on ADG of broiler chickens.

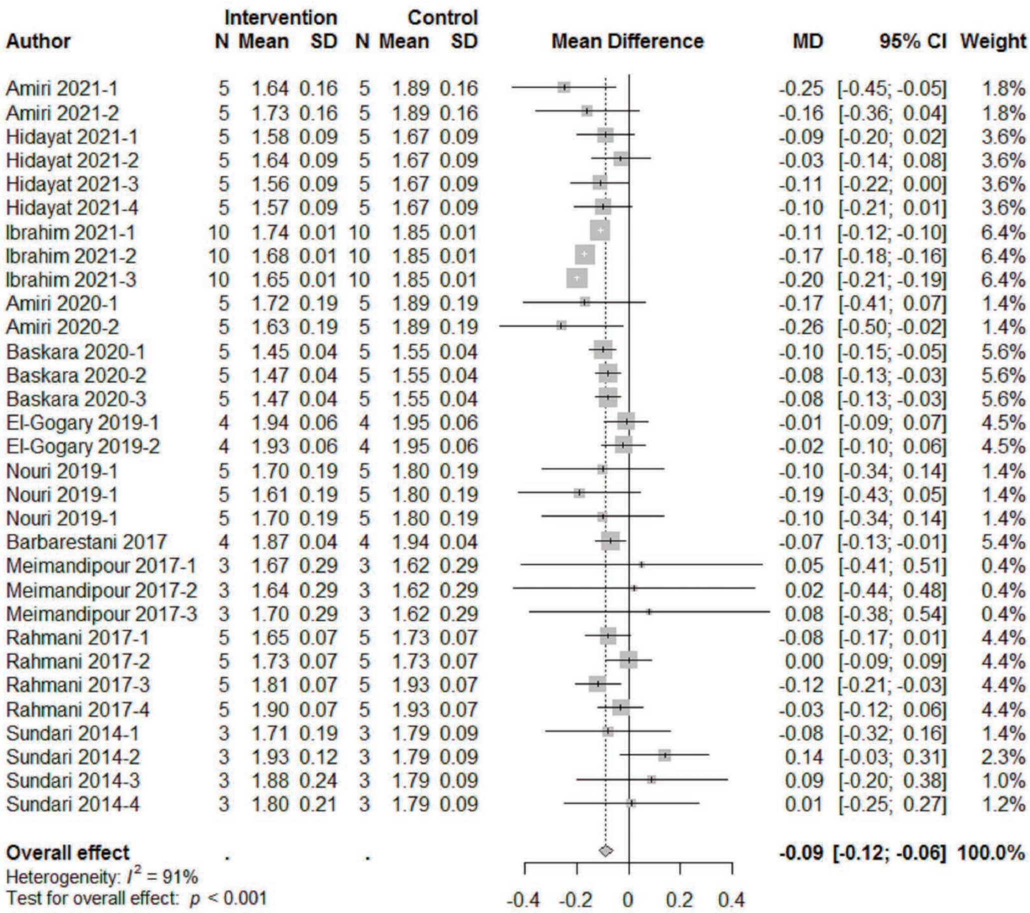

Fig. 4. Forest plot of the effect of nano-phytobiotics inclusion on FCR of broiler chickens.

not significantly associated (P>0.05) with nano-phytobiotics dose and study duration.

Sensitivity analysis

Sensitivity analysis showed that omitting of each of single study at a time did not substantially change the overall effect of ADFI, ADG, and FCR.

Discussion

In the last decade, the use of nano-phytobiotics in poultry nutrition become popular as an alternative to AGP. This study is the first meta-analysis reporting the efficacy of nano-phytobiotics to improve growth performance of broiler chickens. Data synthesis from this study indicate that nano-phytobiotics inclusion in broiler chickens' diet could effectively improve ADG and FCR with comparable ADFI. This finding again strengthens the previous evidence showing the efficacy of phytobiotics to improve growth performance of broiler chickens (Andri *et al*., 2020b; Irawan *et al*., 2020; Ogbuewu and Mbajiorgu, 2020; Ogbuewu *et al*., 2020a; Prihambodo *et al*., 2021).

The growth promoting effect of nano-phytobiotics in broiler chickens probably related with antimicrobial and antioxidant properties as their main mechanism of actions. Previously, it has been reported that bioactive compounds in phytobiotics had antimicrobial activity against common poultry pathogens such as *Escherichia coli*, Salmonella sp., and Clostridium perfringens (Sugiharto, 2016; Kiczorowska *et al*., 2017; Gheisar and Kim, 2018; Filazi and Yurdakok-Dikmen, 2019; Abd El-Ghany, 2020; Alagawany *et al*., 2021). The use of nanotechnology also provides better antimicrobial action of phytobiotics (Correa-Pacheco *et al*., 2019; Sahyon and Al-Harbi, 2020; Ahmadi *et al*., 2021). In the intestinal environment, there is always a competition of nutrient utilization between the pathogenic bacteria and the host. For that reason, the reduction in the pathogenic bacteria will benefit the host with the higher nutrient availability (Dittoe *et al*., 2018; Fancher *et al*., 2020; Feye *et al*., 2020). Additionally, the use of phytobiotics also associated with the lower gut pH but higher digestive enzyme secretion and activity, which further followed by the improvement in the nutrient digestibility (Olukosi and Dono, 2014; Purwanti *et al*., 2015; Zeng *et al*., 2015; Mohamed *et al*., 2018; Song *et al*., 2018; Basit *et al*., 2020; Sugiharto, 2020; Mohamed *et al*., 2021).

The use of nano-phytobiotics also served as antioxidant sources. Nano-phytobiotics supplementation could improve antioxidant status by improving superoxide dismutase and reduced glutathione but decreasing malondialdehyde concentrations (Heidary *et al*., 2020; Reda *et al*., 2020). The higher antioxidant status may promote better villi development as indicated by the higher villi height (Song *et al*., 2018; Abolfathi *et al*., 2019; Tang *et al*., 2019; Barbarestani *et al*., 2020), which consequently led to the higher absorptive surface area and increased in the nutrient absorption (Ur Rahman *et al*., 2017; Omar *et al*., 2020; Kikusato, 2021). Together, the higher nutrient availability, digestion, and absorption will ultimately be followed by the improvement in ADG and FCR.

It should be underlined that nano-phytobiotics dose and study duration resulting varying degree of growth-promoting effect of nano-phytobiotics. In line with this finding, other studies also observed that the efficacy of feed additives inclusion was varied across treatment dose and study duration (Ogbuewu *et al*., 2020b; Ogbuewu *et al*., 2021). Moreover, it also should be mentioned that the robustness of this current finding is warranted because the overall effect size remained stable after sensitivity analysis test.

Conclusion

This meta-analysis provides evidence that nano-phytobiotics inclusion could improve average daily gain and feed conversion ratio without alter average daily feed intake of broiler chickens. However, their efficacy may vary according to the nano-phytobiotics dose and study duration. The use of nano-phytobiotics is desirable as an alternative to antibiotic growth promoters.

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Conflict of interest

The authors declare no conflict of interest associated with this study.

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