Protective effects of various feed additives on broiler chickens exposed to mycotoxin- contaminated feed: A systematic review and meta-analysis

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Abstract

Mycotoxin contamination in feed a common problem in broiler chickens. The present systematic review and meta-analysis examined the impact of mycotoxin and efficacy of various feed additives on production performance of broiler chickens fed mycotoxin-contaminated diets (MCD). A total of 28 studies comprising 45 mycotoxin-challenged experiments were selected following PRISMA guidelines. Feed additives included in the analyses were commercial mycotoxin binder (CMB), mycotoxin binder (MB), mannan-oligosaccharides (MOS), organic acid (OA), probiotics (PRO), protein supplementation (PROT), phytobiotics (PHY), additive mixture (MIX), and a combination of CMB + other feed additives (CMB+). Random effects model and a frequentist network meta-analysis (NMA) were performed to rank the efficacy of feed additives, reported as standardized means difference (SMD) at 95% confidence intervals (95% CI). Overall, broiler chickens fed MCD had significantly lower final BW (SMD = 198; 95% CI = 198 to 238) and higher FCR (SMD = 0.17; 95% CI = 0.13 to 0.21). Treatments with MB, MOS, PHY, and MIX improved BW of birds fed MCD ($P < 0.05$) but lower compared to CON ($P < 0.05$). The NMA demonstrated that the CMB + was the highest performing additive (P-score = 0.791) to remedy mycotoxicosis. The MOS, MB, and OA also showed high efficacy based. Adverse effects on organ weights were observed on the increase of liver and heart and the decrease of intestinal tract ($P < 0.001$). Altogether, several feed additives may help to ameliorate mycotoxicosis in broiler chickens although the efficacy was low pertaining to the severity of the mycotoxicosis.

1. Introduction

Mycotoxins are secondary fungi or molds metabolites produced by a variety of Aspergillus species (Tolosa and Ruiz, 2021). They commonly contaminate agricultural crops especially corn during harvesting, transportation, processing, or storage (Joseph et al., 2020). Mycotoxin contamination in animal feed is known as a global issue especially for the poultry industry. The latest global mycotoxin survey reported that more than 85% of animal feed samples from 100 countries were contaminated with mycotoxins, the majority of which were aflatoxin B_1, deoxynivalenol, zearalenone, and fumonisins (Gruber-Dorninger et al., 2019). The Food and Agriculture Organization (FAO) also estimated that 25% of the world's crops were contaminated with mycotoxins (Eskola et al., 2020). A significant economic loss in broiler farm and adverse effects of mycotoxins on growth, immunity, and feed efficiency of broiler chickens have been globally reported. Moreover, the prevalence of mycotoxicosis also impacts on international trade due to the high risk of transfer of toxin residues from food of animal origin (feed-food supply chains) that could impact on the health of people consuming animal products containing mycotoxin residues (Joseph et al., 2020; Tolosa and Ruiz, 2021).

Many adverse effects of mycotoxins have been well documented due to their carcinogenic, mutagenic, and teratogenic characteristics (Magnoli et al., 2010; Murugesan et al., 2015). In broiler chickens, studies have reported that feed contaminated with mycotoxins suppressed immune and liver functions (Bovo et al., 2015; dos Anjos et al., 2015; Magnoli et al., 2017) and decreased intestinal epithelium predisposing to the incidence of necrotic enteritis (Antonissen et al., 2015), that ultimately decreased final body weight (BW) and feed efficiency (Malekinezhad et al., 2021; Nazarizadeh et al., 2019; Poloni et al., 2020; Rashidi et al., 2020). When animals are exposed to mycotoxins, toxic metabolites of mycotoxins are formed in the gut following enzymatic and microbial transformation processes after being ingested. The metabolites are then absorbed via the bloodstream, metabolized in the liver and transiently interact with liver enzymes especially cytochrome p450 system and are then either excreted via urine and feces, or resided in body tissues causing various adverse consequences (Tolosa and Ruiz, 2021).

Several preventive actions via routine monitoring of mycotoxins in raw materials of feed have been developed (Cheli, 2020; Fumagalli et al., 2021) while a variety of dietary interventions on farm have also been introduced to minimize the serious impacts of mycotoxins. Mycotoxin binders (MB) are commercially available products that are the most frequently used by poultry farmers because they are able to form stable-nontoxic metabolites thus reducing the toxicity (Lee et al., 2012; Tavangar et al., 2021). In addition, a large number of articles have also discussed the effect of feed additives including probiotics (PRO) (Rashidi et al., 2020; Zuo et al., 2013; Ardiansyah et al., 2022), prebiotics (Bovo et al., 2015; Soltani et al.,

2019), essential oils or other various types of phytogenic additives (Armanini et al., 2021; Tavangar et al., 2021), organic acids (Salgado-Tránsito et al., 2011), and protein supplementation (Attia et al., 2016, 2013) to prevent more serious chronical effect. Along with the increasing scientific evidence of the effect of feed additives on mycotoxicosis, different efficacy was identified depending on types of additives or types of mycotoxin binders and mycotoxins used to contaminate the feed. For instance, degree of recovery of different commercial mycotoxin binders on broiler fed diets contaminated with ochratoxin and/or T2 varied between 75 to 96% (García et al., 2003) while another study reported a recovery rate of 85% on aflatoxin B1 contaminated diet (Nazarizadeh and Pourreza, 2019). In a comparative feed additives study, plant extract rich in antioxidant demonstrated the highest recovery rate compared to probiotics, commercial toxin binders, and biochar (Rashidi et al., 2020). Other numerous studies also indicated a non-conclusive efficacy.

Review articles are available that comprehensively discuss the positive outcomes of various dietary strategies to reduce the toxic effect of mycotoxins in broiler chickens (Fouad et al., 2019; Joseph et al., 2020; Rawal et al., 2010). However, lack of global quantitative evidence of the efficacy of various additives on mycotoxin-contaminated feed in broiler chickens warrants a comprehensive investigation using a systematic approach, i.e., meta-analysis. Additionally, even though above meta-analyses could provide a meaningful interpretation, network meta-analysis would be useful to elucidate the effectiveness of various types of additives being used as a treatment for mycotoxin in broiler chickens. This is especially important because each study was designed using different additives. Thus, head-to-head comparison using subgroup meta-analysis might not powerful. Our study attempts to quantify the impact of mycotoxin on broiler production and examines the effectiveness of various feed additives to ameliorate mycotoxicosis in broiler chickens.

2. Materials And Methods

2.1. Search of literature

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) checklist was used as a guideline for meta-analysis. A systematic literature search was performed on well-respected databases including Web of Science, Scopus, Science Direct, and PubMed Central to generate reliable studies published between 1980 and May 12th 2022. Keywords used were as follows: "mycotoxins" [MeSH Terms] OR "mycotoxins" [All Fields] OR "mycotoxin" [All Fields]) AND ("aflatoxins" [MeSH Terms] OR "aflatoxins" [All Fields] OR "aflatoxin" [All Fields]) AND Broiler chicken [All Fields] AND Additive [All Fields]. One researcher conducted the searches, imported the titles' outcome, and first-screened the title for article duplication within databases. The generated titles were then examined by two independent researchers for further selection process.

2.2. Eligibility and selection process

Restriction was applied to only original articles with English language without limited to publication year. Thus, review, non-peer-reviewed articles including proceedings, and gray literatures were removed from the database. The title of publications were managed with the aid of Mendeley reference manager and the titles' evaluation was performed strictly using the inclusion criteria as follows: (1) randomized trial conducted in vivo using broiler chickens; (2) examines the use of additive and/or mycotoxin binders in a mycotoxin-challenged diet; (3) reports performance data such as body weight (BW) or daily gain (ADG), feed intake or feed conversion ratio (FCR); (4) explicitly reports the type of additive and type of mycotoxin used. Titles were excluded if they were conducted *in vitro* or laboratory testing of mycotoxin without *in vivo* experiment. Field surveillance and quantitative assessment or estimation (not directly measured) were also removed from the database. Supplementary search from cited references of the selected studies was conducted to anticipate if we fail to hit other relevant studies during the searching. Final lists of titles were downloaded for full text evaluation. Five investigators were involved in the selection, extraction, validation, and standardization processes. Any disagreement was discussed and resolved.

In this meta-analysis, additive and mycotoxin levels added to the diets were not considered for examination since their levels were mostly pre-determined for their optimum doses. In addition, the purpose of this study was exclusively to examine the efficacy of different types of feed additives. A total of 28 studies comprising of 40 experiments met the criteria and were extracted in a customized spreadsheet. Details of selection process is outlined in Fig. 1 and final studies used for meta-analysis are summarized in Table 1.

Table 1
List of studies

No	Study	Year	Country	*N* Exp	*N* bird	Strain	Rearing period (d)	Additive	Mycotoxin
1	(Dale et al., 1980)	1980	Georgia	1	48	NA	28	Tannic acid	AF
2	(Abdelhamid et al., 1994)	1994	Egypt	2	240	Lohmann	42	+Protein or + ME	AFB_1
3	(Raju and Devegowda, 2000)	2000	India	3–7	768	NA	35	Esterified-glucomannan	AFB_1, OA, T-2
4	(Diaz et al., 2005)	2005	Columbia	8	180	Ross	28	Mycotoxin binder (Mycofix Plus; Mycosorb; MycoAd; Zeolex)	T-2
5	(Girish and Devegowda, 2006)	2006	India	9–11	720	NA	35	Humic acid	AFB_1, T-2
6	(Jansen Van Rensburg et al., 2006)	2006	South Africa	12	420	Ross	42	Mycotoxin binder (Mycosorb); HSCAS	AFB_1
7	(Abousadi and Honarmand, 2007)	2007	Iran	12	320	Ross	28	Formicine; HSCAS; MB (Toxiban); Saccharomyces cervisiae; Sodium bentonite; Ammonia	AFB_1
8	(Pasha et al., 2007)	2007	Pakistan	1317		NA	22	Sodium bentonite; Gention violet; Acetic acid; MB (Sorbatox; Klinofeed)	AF
9	(Salgado-Tránsito et al., 2011)	2011	Mexico	18	375	Ross	28	Citric acid	AFB_1, AFB_2
10	(Chand et al., 2011)	2011	Pakistan	19–20	240	Starbrow	35	MB (Mycoad); Milk Thistle	AFB_1
11	(Magnoli et al., 2011)	2011	Argentina	21	200	Cobb	33	Sodium bentonite; Monensin	AFB_1
12	(Attia et al., 2013)	2012	Egypt	22–24	88	Cobb	21	MOS; HSCAS; Probiotics	AFB_1
13	(Zuo et al., 2013)	2013	China	25	75	Arbor Acres	30	Probiotics (LAB)	AFB_1
14	(Kumar Dhanapal et al., 2014)	2014	India	26	160	Ross	28	Citrus fruit oil	AFB_1

HSCAS = Hydrated sodium calcium aluminosilicate; LAB = Lactic acid bacteria; MB = Mycotoxin binders; ME = metabolizable energy; MOS = mannan oligosaccharides

AFB_1 = Aflatoxin B_1; AFB_2 = Aflatoxin B_2; OA = ochratoxin A; T2 = Toxin-2 mycotoxin

No	Study	Year	Country	*N* Exp	*N* bird	Strain	Rearing period (d)	Additive	Mycotoxin
15	(Sridhar et al., 2015)	2014	India	27	120	Cobb	42	Phytobiotics (not specified)	AFB_1
16	(Oliveira et al., 2015)	2015	Brazil	28	576	Cobb	21	MOS	AFB_1
17	(Fowler et al., 2015)	2015	USA	29–31	336	Ross	21	Calcium bentonite	AFB_1
18	(Attia et al., 2016)	2016	Egypt	32–34	200	Cobb	21	MOS; HSCAS; Probiotics (LAB)	AFB_1
19	(Magnoli et al., 2017)	2017	Germany	35	160	Cobb	21	Sodium bentonite; Monensin	AFB_1
20	(Al-Zuhariy and Hassan, 2017)	2017	Iraq	36	250	Ross	21	Ganoderma lucidum; Andrographolide; Turmeric curcuma	AFB_1
21	(Abdel-Sattar et al., 2019)	2019	Egypt	36	210	Arbor Acres	35	+Protein; HSCAS	AFB_1
22	(Soltani et al., 2019)	2019	Iran	37–38	600	Ross	42	MB (Mixed of Bentonite, yeast wall, organic acid and vitamins)	AFB_1
23	(Nazarizadeh et al., 2019)	2019	Iran	39–40	720	Ross	28	Phytobiotics (Chamomile flower extract; Thyme- oil extract)	AFB_1, OA
24	(Rashidi et al., 2020)	2020	Iran	41	504	Ross	42	Licorice extract; Probiotic (LAB); MB Biochar	AFB_1
25	(Armanini et al., 2021)	2021	Brazil	42	160	Cobb	34	Phytobiotics (Acidosan®)	AF
26	(dos Santos et al., 2021)	2021	Brazil	43	288	Cobb	21	MOS	AFB_1
27	(Tavangar et al., 2021)	2021	Iran	44	250	Ross	35	Phytobiotic (Entex); MB (Mycofix Plus)	AFB_1
28	(Malekinezhad et al., 2021)	2021	Iran	45	450	Ross	42	Berberine Alkaloid	AFB_1, OA

HSCAS = Hydrated sodium calcium aluminosilicate; LAB = Lactic acid bacteria; MB = Mycotoxin binders; ME = metabolizable energy; MOS = mannan oligosaccharides

AFB_1 = Aflatoxin B_1; AFB_2 = Aflatoxin B_2; OA = ochratoxin A; T2 = Toxin-2 mycotoxin

2.3. Data extraction

Information of authors, year, journal information details, birds' strain and n birds per group of treatment, country of origin, n replicate, rearing period, feed composition, group of treatment details, type of additive and its administration level, type of mycotoxin and its contamination dose, and all response variables reported in the article were extracted and integrated into the dataset. Graphical data were extracted using an online tool of WebPlotDigitizer (https://apps.automeris.io/wpd/)

(Irawan et al., 2022, 2021). Studies containing more than one *in vivo* experiment were encoded separately. Cross-validation was performed by two other independent researchers to assure the validation of information given. Data with different measurement unit were standardized into similar measurement unit. In addition, calculations were also made for outcome variables such as intake, ADG/BW, and FCR by using available data that can be used to do so (Rusli et al., 2022).

2.4. Outcomes

The primary outcomes were productive performance of broiler chickens including body weight, average daily gain, feed intake, and feed conversion ratio (FCR). The secondary outcomes examined in the present meta-analysis were organ weights (liver, heart, gizzard, and intestine), blood biochemistry profile (glucose, triglycerides, cholesterol, total protein, albumin, globulin, creatinine), and liver enzyme activity (AST, ALT, ALP).

2.5. Publication bias

Study limitation, also popularized as risk of bias from individual study was examined following the Cochrane collaboration assessment (Higgins et al., 2011). Evaluation was performed by using several criteria for each study including (1) randomization and animal handling; (2) methods and measurements; (3) statistical approach; (4) result variances; and (5) measurement outcomes. Two independent researchers were involved in this assessment and they were finally validated by one researcher. For each criterion, hierarchical judgements were used as a “low risk” and was given a score of 3, “some concerns” given score of 2, and “high risk” given score of 1, and were finally pooled as an overall risk of bias result. Studies that had a total score of ≤ 7 were excluded from the analysis (Zhou et al., 2022). A summary table containing individual study assessments was submitted to the robvis (Risk-of-bias VISualization) website to generate the traffic light plots and weighted bar plots (Mcguinness and Higgins, 2021) as illustrated in Fig. 2.

2.6. Data synthesis and meta- analysis

We initially grouped the data into three group of treatments based on characteristics of most the challenged-studies; (1) control group [CON] – broiler chickens without receiving any dietary treatment, (2) mycotoxin-contaminated diet [MCD] – broiler chickens fed mycotoxin-contaminated diet, (3) feed additives added onto the MCD (TRT) – broiler chickens fed MCD plus supplemental additive; and (4) FAS – feed additives supplemented to CON group. Furthermore, types of additives were further classified as a different group of treatments considering that there were various additives used as a strategy to ameliorate the negative effect of aflatoxin contaminated diet. Feed additives that were included in the analyses were commercial mycotoxin binder (CMB), mycotoxin binder (MB), mannan-oligosaccharides (MOS), organic acid (OA), probiotics (PRO), protein supplementation (PROT), phytobiotics (PHY), additive mixture (MIX), and a combination of CMB + other feed additives (CMB+). Principal component analysis (PCA) was firstly carried out to reduce the data dimension from wide variation of types of additives and group of treatments by using FactoMineR package in R (Le et al., 2008). Using the Eigenvalue > 1 as a cutoff criterion, the principal components were plotted to describe the principal components associated with the treatment as well as the paternal effects of the type of additives on production performance of broiler chickens.

Furthermore, two types of meta-analysis were performed to estimate the efficacy of various additives to remedy mycotoxicosis in broiler chickens. First meta-analysis was based on continuous data design that were analyzed using a random effect model (REM) with sub-group meta-analysis evaluation to discriminate groups and types of additive effects. The REM was chosen because it is powerful in handling data with heterogeneity evidence ($Q < 0.05$; $I^2 > 50\%$) (Lin et al., 2022). In this analysis, means with their corresponding variance (SD) within groups were used to calculate the Hedges' *g* effect size using the formula of:

$$g \cong d \times (1 - \frac{3}{4\,(n1 + n2) - 9})$$

Where *n* is the sample size from each group (Higgins et al., 2003). The standardized means difference (SMD) was used to express the pooled effect size obtained above and was summarized in a forest plot with 95% confidence intervals (CIs). Hedges' *g* was chosen because it has strong analytical power for meta-analysis with relatively small sample size (Galkanda-Arachchige et al., 2020). The 95% CI estimate of Hedges' *g* without 0 overlapped ($P \leq 0.05$) indicates a significant effect of the treatment groups compared with control. The "metafor" package in R was used for the random effects model analysis (Viechtbauer, 2010).

2.7. Assessment of heterogeneity

Several sources of heterogeneity were considered including countries, dietary intervention groups (CON, MCD, TRT), and the types of feed additives. Cochran's Q statistic and I^2 statistic were adopted to quantitatively assessed heterogeneity. Among all studies, heterogeneity was categorized as a high ($I^2 \geq 75\%$), moderate ($50\% < I^2 \leq 75\%$), low ($25\% < I^2 \leq 50\%$), and no evidence of heterogeneity ($0 < I^2 \leq 25\%$) (Higgins et al., 2003). Once high heterogeneity was identified, sensitivity analysis using leave-one-out analysis was performed to identify studies potentially to be excluded due to high heterogeneity source (Xu et al., 2020).

2.8. Meta-regression

Second, meta-regression analysis was performed by using a mixed model methodology (St-Pierre, 2001) in SAS to depict the relationship between feed intake (FI) and body weight (BW) gain for each condition (group of treatments). This analysis allowed the prediction of BW outcome as explained by the three different scenarios (groups) with the following models:

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 X_i^2 + (\beta_1 \times \beta_3) Xi \times s_i + b_i X + \varepsilon_i,$$

where Yi = estimated BW outcome as the dependent variable, β0 = estimated overall intercept (fixed effect), β1 = coefficient of linear regression model from the feed intake (fixed effect), β2 = coefficient of quadratic regression model from the feed intake (fixed effect), β1 × β3 = interaction effects between feed intake and group of treatment, Xi = feed intake level as a continuous predictor variable, si = the random effect of the study, bi = the random effect from study on the regression coefficient of Y on X, and εi = the residual error at ~ N(0,σ2). The number of replications was used as a weighting factor in the model. As described by (St-Pierre, 2001), adjusted Y values were calculated by adding the predicted values of Y and their corresponding residual values to generate the regression line.

2.9. Network meta- analysis

A frequentist network meta-analysis was performed using a "*netmeta*" package in R which basically examines the probability of event E in experiments S by employing the effect size (SMD) data obtained from random effect meta-analysis as conducted earlier. The effect size was calculated using the following model:

$$\theta = X\theta_{treat} + \boldsymbol{\epsilon}$$

Where the estimated effects size θ is a vector obtained from the $X_{(m \times n)}$ matrix where *m* is the treatment comparison and *n* represents the treatment groups. θ_{treat} is the vector of estimated true effect size in the network that allows us to predict the most effective additive treatments and ϵ is the error term. A network graph illustrates the comparisons being made among the additives, control diet, and MCD. Further, treatment rankings among the additives were calculated using the "netrank" function where the ranking output was indicated as a P-scores (SUCRA score in Bayesian NMA) and then were illustrated in a forest plot. Heatmap plot was produced to further examine the degree of inconsistency in the built network. Colored backgrounds indicate a strong inconsistency (red to blue as the highest to the lowest) and the gray background indicates the importance of the comparison (greater = more important).

3. Results

3.1. Description of dataset

Together, 28 studies comprising of 45 experiments were integrated with 8,658 broiler chickens were included. All studies employed randomized control trials (RCT) using sufficient number of birds per replicate (≥ 10 birds). The studies represent 14 countries across the world including African countries (South Africa, Egypt), North and South America (The USA, Mexico, Columbia, Brazil, Argentina), Europe (Germany, Georgia), and Asian (China, India, Iran, Iraq, Pakistan). The experiments were predominantly conducted using Ross (43.9%) and Cobb (28.6%) and the birds were mostly unsex as commonly obtained from broiler breeder company. Among all challenged studies, we identified four types of mycotoxins being incorporated into the diets as a challenged model including aflatoxin B_1 (AFB_1), aflatoxin B_2 (AFB_2), ochratoxin (OA), and T2 toxin-2 (T2). AFB_1 is the most predominant toxin which represents 27/28 studies, consisting of 19 studies used only AFB_1 and the others were in combinations with either OA, T2, or AFB_2. Only one study used T2 as a contaminant and one study used a combination of three (AFB_1 + OA + T2). The diverse feed additives were identified throughout the experiments as dietary interventions strategy. These include various CMB (Mycofix Plus, Mycosorb, MycoAd, Zeolex, Toxiban, Sorbatox, Klinofeed) and other specified as MB (milk thistle, sodium bentonite, calcium bentonite, humic acid), PHY (tannic acid, citrus fruit oil, turmeric extract, thyme oil extract, licorice extract, berberine alkaloid, and others commercially available photobiotic), PRO, MOS, and also high-density nutrient diets through supplementary amino acids, protein (PROT) and energy. Several studies used a combination of feed additives such as MOS + phytogenic feed additives + organic acid + probiotics; this was categorized as “MIX” in the dataset while studies with a combination of MCB with other feed additives were encoded as CMB+. All details of the experimental treatments are available in Table 1. The individual additive was encoded and included in the analyses when the sample size is sufficient (n ≥ 3 studies).

Nutrient specifications of the included studies were according to nutrient standards in most of strains of broiler chickens for ME, CP, lysine, and methionine (Table 2). There were large variations on the descriptive statistics of performance, blood biochemical profiles, and liver enzymes activities as they were influenced by mycotoxins challenged and dietary treatments. The variations on performance data were related to the different rearing periods among studies included in this meta-analysis.

Table 2
Descriptive statistics of the dataset

Parameters	Unit	*N*	Mean	SD	Min	Max
Nutrient composition of diets						
ME	Kcal/kg	65	3042	65.9	2909	3150
CP	%	65	21.5	1.33	18.6	24.0
Lysine	%	69	1.24	0.12	1.03	1.50
Methionine	%	59	0.48	0.09	0.36	0.62
Performance						
Feed intake	g/d	151	71.8	22.1	21.0	119
FCR		183	2.84	12.9	1.28	176
ADG	g/d	106	43.1	15.4	15.2	82.5
Body weight	g	171	1245	685	1.25	2675
Blood biochemistry profile						
Glucose	mg/dL	18	179	22.4	148	211
Triglycerides	mg/dL	33	93.1	54.2	6.90	175
Cholesterol	mg/dL	51	114	40.2	45.6	183
Total protein	g/dL	81	3.35	1.24	1.09	6.30
Albumin	g/dL	52	3.03	3.31	0.97	15.2
Globulin	mg/dL	24	2.12	0.37	1.31	2.68
Creatinine	mmol/L	22	0.50	0.40	0.18	1.80
Liver enzyme activity						
AST	mg/dL	76	133	78.00	20.9	301
ALT	mg/dL	67	11.4	9.87	1.33	55.5
ALP	I.U	39	828	909	5.00	3828
Organ weight						
Liver	% BW	108	3.08	0.82	1.87	5.34
Heart	% BW	45	0.67	0.17	0.37	1.10
Gizzard	% BW	69	3.98	3.15	1.35	17.0
Intestinal	% BW	28	8.92	4.32	3.53	16.6

ADG = average daily gain; ALP = Alkaline Phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; CP = crude protein; FCR = feed conversion ratio; ME = metabolizable energy; N = number of data point; SD = standard deviation

3.2. Publication bias and heterogeneity test

Quality assessment of publication bias showed that all studies included in the analysis had ≥ 7 of quality score and therefore were deemed of high quality. Overall judgement resulted in 22 studies with low publication bias and 6 studies with moderate publication bias (Fig. 2).

The heterogeneity test showed that the I^2 was more than 50% in most outcomes with significant Q statistics ($P < 0.01$), indicating that the studies were heterogenous even in subgroup meta-analysis. Only few outcomes had $I^2 < 50\%$ such as subgroup analysis of ADG, effect of additive supplementation on albumin and creatinine. Considering the evidence of significant heterogeneity, the REM was chosen for meta-analysis. No evidence of significant effect within the studies obtained from leave-one out sensitivity analysis and therefore the data were all used in the analyses.

3.3. Performance

Two principal components of dietary treatments on performance data were able to explain 88.62% of the total variance where the PC1 represents 62% of the variance. This approach, unfortunately, was not able to distinguish the clusters between dietary condition and performance data as they shared similar patterns. PCA plot based on the type of feed additives showed that the CMB had a different cluster from the other additives. In addition, MCD showed a cluster that follows the direction of FCR. Overall, the patterns observed from the PCA (Fig. 3) were not fully powerful to capture the efficacy of feed additives toward mycotoxin diets. Probably, more specific dataset with larger sample size would be useful to provide a meaningful pattern.

Forest plot (Fig. 4) summarizes subgroup meta-analysis based on random effect models of dietary interventions on performance data of broiler chickens. It showed that broiler chickens fed MCD had a significant reduction in their ADG (SMD = -5.691; 95% CI = -9.307 to -2.074; $P < 0.001$), FI (SMD = -11.718; 95% CI= -13.59 to -9.845; $P < 0.001$), and feed efficiency as shown in the higher FCR (SMD = 0.166; 95% CI = 0.127 to 0.206; $P < 0.001$). Broiler chickens fed MCD had lower BW, averaging by 198.2 g (95% CI = -238.43 to -157.92; $P < 0.001$) than the control diet. Treatments using feed additives, regardless of type of additives, was able to minimize the suppression effects of mycotoxins as shown by the lower SMD on ADG, BW, and FI when compared to mycotoxins diets, although it was significantly lower compared with control. In addition, the effect of FAS was similar to the CON group in growth performance of broiler chickens ($P > 0.10$), due to large variances of additive types being used.

Furthermore, subgroup analysis based on type of additives used to minimize mycotoxins effect on performance data is displayed in Fig. 5. Overall, they were able to increase BW but difference degree of efficacy was observed. PHY, MIX, MOS, CMB, and MB were effective to reduce the adverse effects of mycotoxins on BW ($P < 0.01$). All types of additives also showed a significantly higher FI ($P < 0.05$) than that of mycotoxin diets except PRO ($P > 0.05$). Several feed additives such as PRO, PROT, MOS, and OA had a positive effect to lower ($P < 0.05$) the FCR while the other did not affect the FCR ($P > 0.05$).

Figure 6 depicts the comparative relationships between feed intake and final BW of broiler chickens in response to different dietary interventions. As normally expected in broiler chickens, all growth patterns follow curvilinear model. Although the sample sizes were different among the diet groups that may limit the comparison, it was observed that those groups had distinct models as shown by their intercepts and slopes. The MCD had lower slope compared with CON and TRT. Predictions from the generated equations on final BW based on standard feed intake provided by Cobb-vantress (Cobb500™ Broiler) on 35 d of harvesting resulted in significantly lower (-264 g) final BW for broiler chickens exposed to mycotoxins diet when compared to CON. Meanwhile, feed additives that were added to MCD could alleviate the final BW to be 164 g higher than that of MCD group (-99.6 g lower than control) while the additive group was 24.2 g higher than control, as expected.

3.4. Organ weight

Broiler chickens fed MCD demonstrated liver necrosis and other organ damages (Table 3). As the principal target organ of aflatoxin, significantly higher weight of liver was observed (SMD = 0.75; 95% CI = 0.62–0.89, P < 0.001), even though therapeutic treatments were conducted (SMD = 0.53; 95% CI = 0.45–0.60; P < 0.001). The weights of gizzard and heart were found to increase (P < 0.001) by MCD while TRT group had no effect on the gizzard weight. Moreover, intestinal weight of broilers significantly decreased in MCD (SMD = -0.99; 95% CI = -4.40 to 2.43; P < 0.001) compared to CON. The TRT group showed non-significant effect on the weight of intestine compared with control (P = 0.09), an indication that feed additive added to MCD was able to recover the enlargement effect of mycotoxin in the intestine.

Table 3
Subgroup meta-analysis comparing the effect of mycotoxin-contaminated diet and the efficacy of additive treatment on organ weight of broiler chickens

Subgroups	*N*	Random effect model (CI 95%)			SE	P-value	Heterogeneity	
		SMD	Lower	Upper			I^2	*Q*
Liver								
Mycotoxin-challenged	25	0.75	0.62	0.89	0.069	< 0.001	99.51	< .0001
Additive treatment	59	0.53	0.45	0.60	0.038	< 0.001	99.09	< .0001
Additive supplementation	10	-0.19	-0.34	-0.05	0.072	0.007	98.09	< .0001
Overall	94	0.53	0.46	0.61	0.037	< 0.001	98.50	< .0001
Gizzard								
Mycotoxin-challenged	16	0.81	0.65	0.96	0.080	< 0.001	99.87	< .0001
Additive treatment	39	0.84	0.59	1.09	0.128	< 0.001	99.95	< .0001
Additive supplementation	6	0.14	0.01	0.28	0.068	0.064	86.65	< .0001
Overall	61	0.77	0.62	0.91	0.075	< 0.001	99.94	< .0001
Intestine								
Mycotoxin-challenged	4	-0.99	-4.40	2.43	1.742	0.570	97.87	< .0001
Additive treatment	15	-0.44	-0.95	0.07	0.260	0.090	95.01	< .0001
Additive supplementation	5	-2.61	-4.31	-0.91	0.867	0.003	89.15	< .0001
Overall	24	-0.98	-1.52	-0.43	0.279	< 0.001	96.21	< .0001
Heart								
Mycotoxin-challenged	8	0.04	0.02	0.05	0.008	< 0.001	98.71	< .0001
Additive treatment	25	0.01	0.01	0.01	0.002	< 0.001	96.10	< .0001
Additive supplementation	6	0.02	0.00	0.03	0.008	0.077	81.09	< .0001
Overall	39	0.01	0.01	0.02	0.002	< 0.001	96.80	< .0001

I^2 = heterogeneity within-studies used in meta-analysis; *Q* = p-value for *Q* statistics; CI = confidence interval at 95% (lower and upper); *n* = sample size; SE = standard error; SMD = standardized means difference

Subgroups consisted of Mycotoxin-challenged = diet contaminated with mycotoxin; Additive treatment = diet contaminated with mycotoxin + feed additives to treat mycotoxicosis; Additive supplementation = control diet without mycotoxin contamination + feed additives

3.5. Blood biochemistry profiles

Mycotoxin had no effect on blood glucose and globulin concentrations while it affected blood protein, albumin, triglycerides (TG), and cholesterol (CH) to be significantly lower (Table 4) compared with control diet. On the other hand, serum creatinine increased in broiler fed MCD (SMD = 0.27; 95% CI = 0.14 to 0.39; P < 0.001). As expected, increased in AST (SMD = 37.26; 95% CI = 13.32 to 61.21; P < 0.001) and ALT (SMD = 3.93; 95% CI = 2.62 to 5.25; P < 0.001) activities were found when the birds were exposed to MCD. The increased was related to the liver functions damage. TRT group helped to reduce oxidative stress biomarkers of AST to be non-significantly different with control diet (SMD = 4.52; 95% CI = -0.85 to 9.88; P = 0.099) and decreased ALT levels (SMD = -3.16; 95% CI = -4.42 to -1.90; P < 0.001). However, the TRT group did not affect the blood biochemical indices such as blood protein, albumin, and TG. Both TRT group and feed additive supplemented to CON had no different on blood glucose, TG, CH, blood protein, and oxidative stress biomarkers (AST and ALT). As a treatment to mycotoxicosis, lower concentrations of blood albumin and globulin concentrations (P < 0.001) were observed when compared with CON. All groups had absence effect on ALP concentration (P > 0.10).

Table 4
Subgroup meta-analysis comparing the effect of mycotoxin-contaminated diet and the efficacy of additive treatment on blood biochemistry profile and liver enzyme activity in broiler chickens

Subgroups	*N*	Random effect model (CI 95%)			SE	P-value	Heterogeneity	
		SMD	Lower	Upper			I^2	*Q*
Glucose								
Mycotoxin-challenged	5	6.20	-2.17	14.57	4.270	0.147	65.16	0.005
Additive treatment	10	-2.85	-7.82	2.12	2.537	0.261	61.63	0.022
Overall	15	-0.10	-4.85	4.65	2.424	0.968	69.98	< .0001
Triglycerides								
Mycotoxin-challenged	9	-3.55	-6.57	-0.53	1.543	0.021	96.03	< .0001
Additive treatment	14	-2.43	-4.17	-0.69	0.888	0.006	91.36	< .0001
Additive supplementation	5	6.46	-2.25	15.18	4.446	0.146	65.16	0.022
Overall	28	-2.05	-3.44	-0.65	0.711	0.004	92.70	< .0001
Cholesterol								
Mycotoxin-challenged	13	-18.91	-30.30	-7.53	5.809	0.001	99.47	< .0001
Additive treatment	26	-4.75	-10.44	0.95	2.908	0.103	98.78	< .0001
Additive supplementation	6	7.28	-8.24	22.79	7.916	0.358	99.15	< .0001
Overall	45	-7.27	-13.28	-1.25	3.069	0.018	99.39	< .0001
Blood Protein								
Mycotoxin-challenged	20	-0.49	-0.72	-0.26	0.118	< 0.001	99.31	< .0001
Additive treatment	36	-0.30	-0.49	-0.10	0.099	0.003	99.17	< .0001
Additive supplementation	7	-0.08	-0.60	0.44	0.264	0.756	98.65	< .0001
Overall	63	-0.33	-0.48	-0.18	0.076	< 0.001	99.33	< .0001
Albumin								
Mycotoxin-challenged	11	-1.08	-1.47	-0.70	0.195	< 0.001	98.77	< .0001
Additive treatment	27	-0.58	-0.74	-0.42	0.083	< 0.001	98.17	< .0001
Additive supplementation	5	-0.09	-0.14	-0.04	0.026	< 0.001	0.00	0.926
Overall	43	-0.64	-0.78	-0.50	0.071	< 0.001	98.33	< .0001
Globulin								
Mycotoxin-challenged	6	0.13	-0.14	0.40	0.137	0.330	85.97	< .0001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; I^2 = heterogeneity within-studies used in meta-analysis; *Q* = p-value for *Q* statistics; CI = confidence interval at 95% (lower and upper); *n* = sample size; SE = standard error; SMD = standardized means difference

Subgroups consisted of Mycotoxin-challenged = diet contaminated with mycotoxin; Additive treatment = diet contaminated with mycotoxin + feed additives to treat mycotoxicosis; Additive supplementation = control diet without mycotoxin contamination + feed additives

Subgroups	*N*	Random effect model (CI 95%)			SE	P-value	Heterogeneity	
		SMD	Lower	Upper			I^2	*Q*
Additive treatment	10	-0.06	-0.18	0.06	0.061	0.358	0.001	0.799
Additive supplementation	4	-0.17	-0.29	-0.05	0.061	0.004	65.45	0.02
Overall	20	-0.02	-0.13	0.08	0.053	0.676	75.54	< .0001
Creatinine								
Mycotoxin-challenged	4	0.27	0.14	0.39	0.063	< 0.001	98.80	< .0001
Additive treatment	13	0.04	0.02	0.06	0.011	0.201	87.73	< .0001
Additive supplementation	2	-0.07	-0.12	-0.01	0.029	0.084	0.001	0.862
Overall	19	0.07	0.04	0.10	0.016	< 0.001	96.22	< .0001
AST								
Mycotoxin-challenged	11	37.26	13.32	61.21	12.22	0.002	99.73	< .0001
Additive treatment	37	4.52	-0.85	9.88	2.737	0.099	98.92	< .0001
Additive supplementation	10	1.56	-2.29	5.42	1.967	0.427	87.14	< .0001
Overall	58	9.14	3.50	14.78	2.878	0.001	99.35	< .0001
ALT								
Mycotoxin-challenged	12	3.93	2.62	5.25	0.671	< 0.001	92.54	< .0001
Additive treatment	35	-3.16	-4.42	-1.90	0.644	< 0.001	99.29	< .0001
Additive supplementation	20	0.20	0.00	0.40	0.103	0.053	18.60	0.272
Overall	57	-1.38	-2.22	-0.54	0.428	0.001	98.99	< .0001
ALP								
Mycotoxin-challenged	9	-166.91	-382.97	49.16	110.24	0.130	15.91	0.311
Additive treatment	18	-57.57	-131.98	16.85	37.967	0.129	95.64	< .0001
Additive supplementation	6	-13.27	-66.92	40.37	27.372	0.628	92.86	< .0001
Overall	33	-77.52	-140.73	-14.31	32.252	0.016	92.65	< .0001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; I^2 = heterogeneity within-studies used in meta-analysis; *Q* = p-value for *Q* statistics; CI = confidence interval at 95% (lower and upper); *n* = sample size; SE = standard error; SMD = standardized means difference

Subgroups consisted of Mycotoxin-challenged = diet contaminated with mycotoxin; Additive treatment = diet contaminated with mycotoxin + feed additives to treat mycotoxicosis; Additive supplementation = control diet without mycotoxin contamination + feed additives

3.6. Network meta-analysis

Frequentist NMA demonstrated that the CMB + were the highest performing additive (P-score = 0.7913; Table 5), indicating that this treatment exhibited the highest recovery rate for BW in broiler chickens compared to the others. Other group of additives such as MOS (P-score = 0.7325), MB (P-score = 0.6737), and OA (P-score = 0.6299) showed high efficacy in ameliorating mycotoxins effects. As visualize in Fig. 7, the forest plot confirms that the ranks of effect sizes of those

additives were higher than that of CON, indicating that they could be good options when dealing with feed exposed to mycotoxins. By contrast, PHY might not be a good option to control mycotoxin contamination as it placed in the lowest rank (P-score = 0.089).

Table 5
P-Score and rank of various additives used to ameliorate toxicity of mycotoxins in broiler chickens based on random effect models of network meta-analysis (mycotoxin-contaminated diets as a reference in the comparisons)

Treatments	P-score	Ranking
Mycotoxin binders + additive	0.7913	1
Mannan oligosaccharides	0.7325	2
Mycotoxin binders	0.6737	3
Organic acid	0.6299	5
Mixed additives	0.4688	6
Probiotic	0.4580	7
Protein supplementation	0.4409	9
Phytogenic	0.0888	10
Number of pairwise comparisons: 152; tau^2 = 0.2917; tau = 0.5401; I^2 = 87.3% [85.5%; 88.9%]		

Additionally, heatmap plot (Fig. 8) helps to identify comparison inconsistency that can may limit the results of the NMA, as shown in the colored background of the plots. In addition, larger grey boxes indicate the more important comparisons between the additives. A red color background is not identified in the heatmap, indicating that the random effect model is appropriate model. Nevertheless, moderate inconsistencies were observed only on few comparisons including CON vs MOS, MCD vs MOS and PHY. Importantly, findings on the high-performing additives match with the importance comparisons showed by the heatmap.

4. Discussion

4.1. Growth performance

Our results revealed overall depressive effects of mycotoxin on reduction of feed intake, final BW, and feed efficiency (increased the FCR). When exposed to mycotoxin, metabolic disturbances occurred which resulting in various clinical signs and diseases (Bryden, 2012). The severe clinical conditions led to decrease in feed intake, nutrient utilization, and impaired growth performance due to the decrease in feed quality, digestive enzymes secretion, and immune system (Bryden, 2012; Malekinezhad et al., 2021; Tolosa and Ruiz, 2021). During immunosuppressive state, nutrients mobilization is directed to develop immune systems rather than is utilized for tissues development or growth. In addition, mycotoxin also impaired the histomorphology of intestinal villi including atrophy, inflammatory infiltrate, and hyperplasia of the goblet cells (Poloni et al., 2020), and therefore digestive enzyme is inhibited (Malekinezhad et al., 2021). These accumulative adverse effects concurrently impaired nutrient absorption, reduced protein synthesis and caused apathy and anorexia (Joseph et al., 2020). As suggested by many researchers, mycotoxins are mostly carcinogenic, and some are teratogenic (ochratoxin A), and mutagenic (AFB_1) (Bryden, 2012; Joseph et al., 2020; Tolosa and Ruiz, 2021).

Our models demonstrated that mycotoxin contamination in feed impaired growth performance of broiler chickens and treatment using feed additives on MCD could help to attenuate the toxicity effects. The different efficacy among feed additives included in the present meta-analysis is attributed to their interactions with mycotoxins in the body of broiler

chickens and their mode of actions. Notwithstanding, it is convincing to perceive that the CMB + was the highest performing treatment to ameliorate the adverse effects of mycotoxin. Regardless of their commercial brands, the commercial products were predominantly formulated by several active ingredients posing high adsorbent capacity against mycotoxins. Moreover, their binding capacity have already examined and passed an array of quality control during manufacturing process. Thus, it is not surprising that those categorized as commercial adsorbents or CMB combined with additives such as phytogenic, MOS, and probiotic demonstrated higher efficacy than other single feed additive. The CMB in the studies was mostly formulated using aluminosilicates which can be one of mycotoxin binders such as bentonites, HSCAS, zeolite, and other types of clay minerals.

The high efficacy of aluminosilicates to remedy mycotoxicosis in broiler chickens was reported by several studies such as 17% ADG improvement (Nazarizadeh & Pourreza, 2017), 15% ADG improvement (Zabiulla et al., 2021), and 21% improvement in body weight (Barrientos-Velazquez et al., 2022), while other study also showed no improvement on the body weight of broiler (Lee et al., 2018). Our meta-analysis showed that commercial mycotoxin binders improved BW by 4.3%. Aluminosilicates are colloidal and clay mineral which can be found in many geographical regions in the world. Their physical structure (porosity, crystal size, and particle size) and high cation exchange capacity promise an excellent capacity as adsorbent for AFB_1 (Nones et al., 2015). In the intestinal tract, they act as detoxifier of toxic metabolites produced by aflatoxin and/or bacteria (Sun et al., 2008). *In vivo* study demonstrated that sodium bentonite could absorb AFB_1 up to 58% in the liver of broiler chickens (Barrientos-velazquez et al., 2022) while *in vitro* binding capacity assays have demonstrated that bentonites were capable to bind nearly 100% of AFB_1 (Diaz et al., 2003).

In addition, MOS was also reported to attenuate adverse effect of mycotoxins by improving secretion of digestive enzyme and immune system (Girish and Devegowda, 2006). Despite the high variability of growth recovery from one to other studies with CMB, as reviewed recently (Fouad et al., 2019), the present findings suggested that available CMB is effective to detoxify mycotoxins contaminant in feed, under recommended doses. Our study also indicated that probiotic, phytogenic, and protein supplementations had very small efficacy to improve growth performance of broiler chickens fed MCD. Although probiotic was suggested to be effective to bind AFB_1, various studies have reported that the binding ability were lower than 80% (Corassin et al., 2013; Fan et al., 2013; Liu et al., 2018; Salem et al., 2018) when compared to MOS (90–100%) and therefore resulting in lower efficacy as found in this meta-analysis. Phytogenic such as essential oil has no direct effect to detoxify mycotoxin since its effect is indirectly based on their antimicrobial and antifungal properties, thus it had little to no role to interact with mycotoxins in the digestive system and/or liver. However, it was suggested to have synergistic effect to higher improvement on growth recovery when added simultaneously with mycotoxin binder as reported recently (Tavangar et al., 2021).

4.2. Organ weight and liver functions

Dataset for organ weight, blood biochemistry, and liver functions was developed from studies using AFB_1 as contaminant. Thus, discussion herein emphasizes on the roles of AFB_1 in affecting organ weight and liver enzymes activities. Our meta-analysis showed a consistent evident that AFB_1 chronically damaged organ functions as indicated by the heavier liver, gizzard, and heart weights. Higher liver weight is among the clinical manifestations that become a visual indicator frequently reported by most previous studies. Broiler chickens exposed to varying levels of AFB_1 showed different degree of liver enlargement from 18.7% with 1.0 ppm (Neeff et al., 2013), to 33.5–34.0% with 0.5 and 2.5 ppm AFB_1, respectively (Gowda et al., 2008; Shannon et al., 2017). However, studies also reported no significant effect by using 0.5 ppm (Rashidi et al., 2020) and 1.0 ppm of AFB_1 (Tavangar et al., 2021). Levels of exposure, age, and physiological status as well as other disease prevalence might explain the discrepancies (Bryden, 2012). The AFB_1 is recognized to have the greatest toxic effect on broiler chickens due to its rapid absorption. Once ingested, it is rapidly absorbed from intestinal tract and interact with albumin and protein and resided in the liver. Liver microsome is responsible to convert the AFB_1 to non-stable toxic metabolites which then covalently bind RNA and alters major biochemical reactions in the liver (Bovo et al., 2015; Tolosa

and Ruiz, 2021). Greater liver weight in birds fed AFB_1 is mainly related to higher lipid accumulation (Rajput et al., 2017; Shannon et al., 2017), due to AFB_1 metabolites binding to DNA, RNA, and protein (Rashidi et al., 2020). Malekinezhad et al. (2021) reported that AFB_1 caused lipid accumulation in the liver, liver yellow pigmentation and enlargement on birds fed AFB_1.

The utilization of non-nutritive feed additive in this meta-analysis, regardless of their types, were able to ameliorate toxicity of AFB_1 at certain degree as shown by the lower SMD compared to MCD. However, literatures suggested that the capability of different feed additives greatly differed depending on specific mode of actions. For instance, by feeding berberine, (Malekinezhad et al., 2021) demonstrated that the liver damage could be ameliorated to be similar with basal diet due to the anti-inflammatory effect of berberine. They suggested that the role of berberine on the reduction of inflammatory cytokine concentrations (IL-6 and TNF-α) is plausible factor for the preventive effect. Moreover, dietary phytogenic resveratrol (Sridhar et al., 2015), hydrate sodium calcium aluminosilicates, *Lactobacillus acidophilus*, MOS (Attia et al., 2013), sodium bentonite, (dos Anjos et al., 2015), and various mycotoxins binders composed from yeast, clay bentonite, and milk thistle (Saleemi et al., 2020) were all effective in reducing liver enlargement effects from AFB_1. Other hand, the use of *Saccharomyces cerevisiae* cells (Bovo et al., 2015) and commercial mycotoxin binders composed from one-single ingredient (Nazarizadeh and Pourreza, 2019) had no effect on relative liver weight on broiler exposed to AFB_1. These data indicated suggested that dietary interventions with additives posing anti-inflammatory properties are more likely to be effective to prevent liver damage due to AFB_1 exposure.

Hepatic injury characterized by the histopathological changes and hepatocytes damages during aflatoxicosis are the primary factors disposing to immunosuppression and oxidative stress experienced by the birds (Armanini et al., 2021; Attia et al., 2013; Magnoli et al., 2010; Poloni et al., 2020; Rajput et al., 2017; Rashidi et al., 2020; Zuo et al., 2013). Histological examinations from documented studies showed that AFB_1 impaired macro- and macroscopic liver appearance such as fatty degeneration, liver vascular changes, necrosis, and bile duct hyperplasia, increased in lymphocyte, heterophil, and eosinophil (Rashidi et al., 2020; Sridhar et al., 2015), accumulatively indicated chronical liver damage. Less functional liver affects protein synthesize as liver is the most responsible organ to produce circulating proteins (Rashidi et al., 2020). Damages in liver functions and architecture inhibit RNA replication and transcription, reduced DNA production and ultimately decreased protein synthesis which then concurrently decrease other blood biochemical indices (Bovo et al., 2015). This was confirmed from the lower blood protein, albumin, and globulin concentrations in this present meta-analysis. AFB_1-contaminated feed studies also reported consistent decreasing effects on blood protein, albumin, and globulin. Challenged with 1.0 ppm of AFB_1 showed to reduce the blood protein by 31.98% (Attia et al., 2013), 36.90% (Bovo et al., 2015), and 38.04% (Rajput et al., 2017), respectively with relatively similar decreasing percentage on albumin and globulin.

Severe metabolic changes in the liver occurred during aflatoxicosis (Bryden, 2012; Tolosa and Ruiz, 2021) such as increase on intracellular production of pro-oxidants such as hydrogen peroxide, superoxide anions and various free radicals. The exceed level of reactive oxygen species (ROS) production, in conjunction with lipid peroxidation produced by AFB_1 depressed antioxidant systems that causing high incidence of oxidative stress in broiler fed aflatoxins diet (Malekinezhad et al., 2021; Rashidi et al., 2020; Sridhar et al., 2015). More consequences are that the decrease on macro- and micronutrients such as vitamins and minerals required by tissues are disturbed (Decoudu et al., 1992). The increased in AST and ALT concentrations were other important liver dysfunction indicators shown from accumulative evidence summarized in our meta-analysis. These liver enzymes are used as biomarker of membrane permeability resulted from liver damage. The elevation is ascribed to hepatocytes damage or cell permeability increase (Rashidi et al., 2020). ALP, on the other hand, was not affected by aflatoxin contamination, similar to previous studies although other liver damage indicators were observed (Attia et al., 2013; Tavangar et al., 2021). Incorporation of feed additives into AFB_1 contaminated diet significantly helped to reduce the AST and ALT concentrations. The preventive mechanisms of feed additive against

liver damage could be direct and/or indirect. The direct effect could be related to the effectivity of the additives especially those with binding and biotransformation capabilities to reduce the harmful effect of the toxic molecules produced by AFB_1 (Rashidi et al., 2020). Indirect effect might be associated with cellular and molecular mechanisms of additive especially those exert anti-inflammatory actions. It was suggested that bioactive compounds such as berberine was able to inhibit AST, ALT, and ALP production via activation of extracellular signal-regulated kinase activity that could inhibit Th17 differentiation. The depression effects on interleukin 17A (IL-17A), IL-6, and TNF-α are part of mechanisms plausibly explaining the anti-inflammatory properties of berberine (Cui et al., 2009; Jakovac et al., 2011; Lou et al., 2011; Malekinezhad et al., 2021).

5. Limitations

Despite sufficient evidence on the efficacy of various additives included in the analyses, it must be noted that several limitations are encountered in the present meta-analysis. First, large variations on the doses of mycotoxins (range between 50 and 3000 ppb) used across studies might resulted in various degree of severity of mycotoxicosis in broiler chickens. Further, it might explain different capability of feed additives to remedy of mycotoxicosis based on the severity experienced by the birds. Effects on different production periods might be detected with more sample size of representative of rearing periods. Due to small numbers of studies using AO and T2, it was not powerful to compare the toxicity within the type of mycotoxins. In addition, data on immunoglobulin, oxidative biomarkers, and intestinal profile were not included in the present meta-analysis due to small number of studies. All the limitations identified in this meta-analysis may provide opportunity to perform further exploration and investigation thus more powerful model can be generated.

6. Conclusion And Implications

Cumulatively, the present meta-analysis provides evidence that mycotoxin-contaminated diet adversely impacts growth performance of broiler chickens. The depressive effects were primarily explained by decrease in feed intake, severe liver damage and dysfunctions, and inhibitory effects on protein synthesis that ultimately alter metabolic and immune systems of broiler chickens. Predictions on final BW from broiler fed mycotoxins-contaminated diet was 13.8% lower than control diet and inclusion of feed additive on the mycotoxins diet, at some point, could ameliorate the depressive effect. The different efficacy of various feed additives was uncovered. Remarkably, our network meta-analysis highlighted higher recovery rates on growth performance when mycotoxicosis was treated using a combination of commercial mycotoxin binders + other types of feed additive such as OA, MOS, or phytogenic additives than single feed additive. MOS and MB such as bentonite, zeolite, and organic acids are the other feed additives showing high efficacy to remedy mycotoxicosis in broiler chickens and therefore can be used as a protective and preventive efforts on farm.

Declarations

Ethics approval

This study utilizes publicly available studies without directly uses human or animal. Therefore, no ethical approval is required.

Declaration of competing interest

The authors declare that they have no financial or personal relationships with other people or organizations that could have appeared to influence the work reported in this paper.

Authors’ contributions statement

All authors contributed to the study conception and design. Material preparation and data collection were performed by Reza Pratama Putra, Dian Astuti, Adib Norma Respati, Niati Ningsih, Triswanto, Aan Andri Yano, and Besse Mahbuba We Tenri Gading. Data curation and data analysis were performed by Anuraga Jayanegara, Mohammad Miftakhus Sholikin, and Agung Irawan. The first draft of the manuscript was written by Reza Pratama Putra and Agung Irawan. Data visualization was performed by Mohammad Miftakhus Sholikin, and Agung Irawan. Hasliza Abu Hassim, Amirul Faiz Mohd Azmi, Danung Nur Adli, and Anuraga Jayanegara reviewed the draft and improved the manuscript. All authors read and approved the final manuscript.

Data and model availability statement

All data included in this study are available upon request by contacting the corresponding author.

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Figures

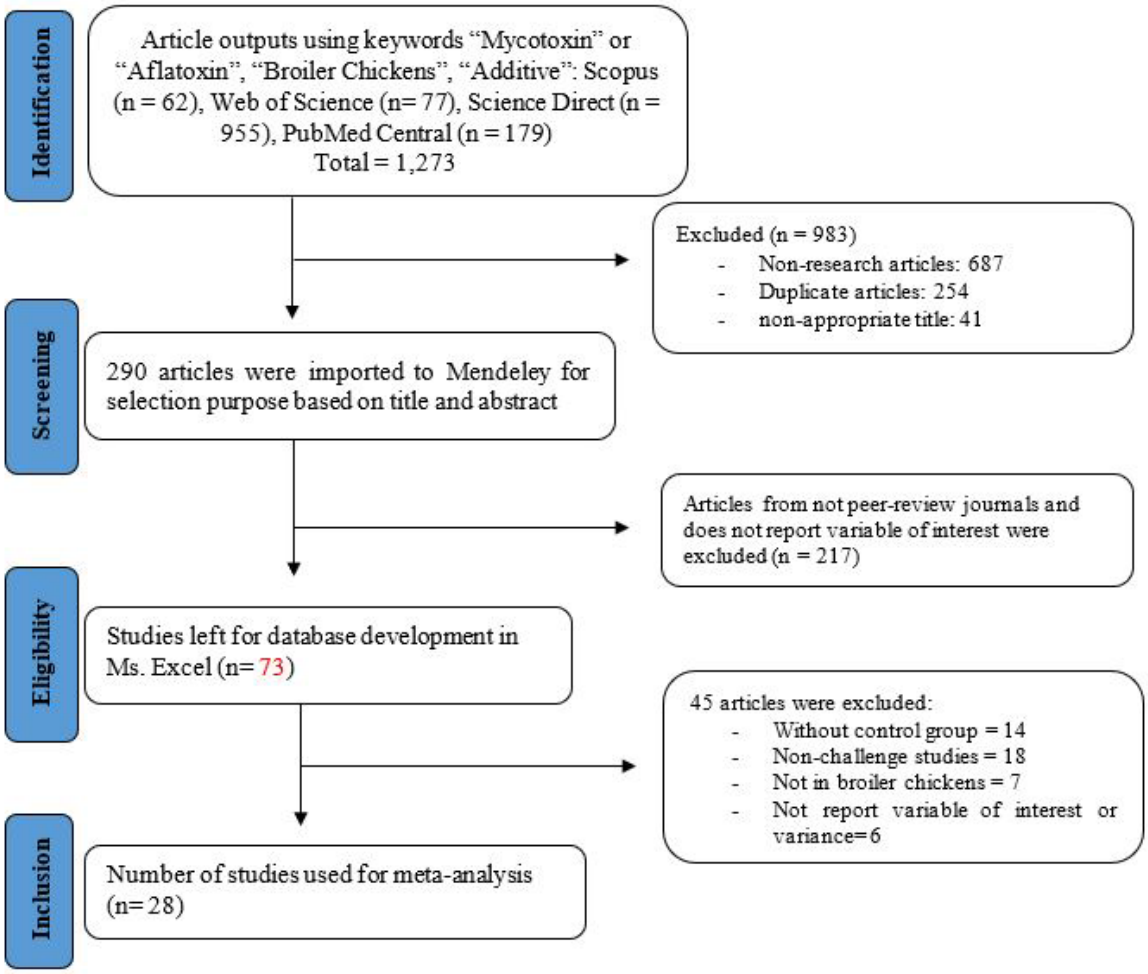

Figure 1

Flowchart of article selection based on PRISMA protocol.

Figure 2

Traffic light plots and weighted bar plots represent the results of risks of bias assessment studies included in the meta-analysis (green means low risk of bias, yellow means unclear risk of bias, red means high risk of bias).

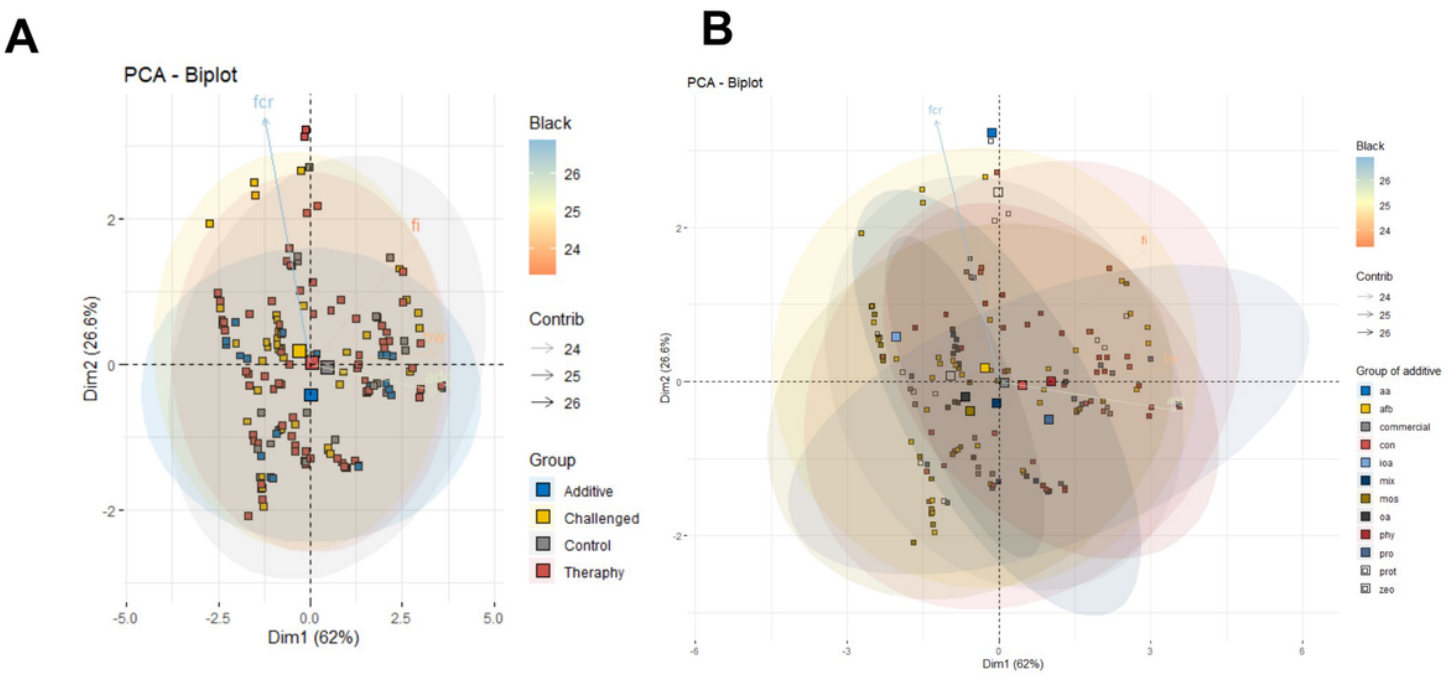

Figure 3

Cluster of type of feed additives discriminated by using Principal component analysis (PCA) based on the growth performance data as response variables. Figure 3A reflects the dietary intervention groups and figure 3B specifically discriminates the types of feed additives as covariate.

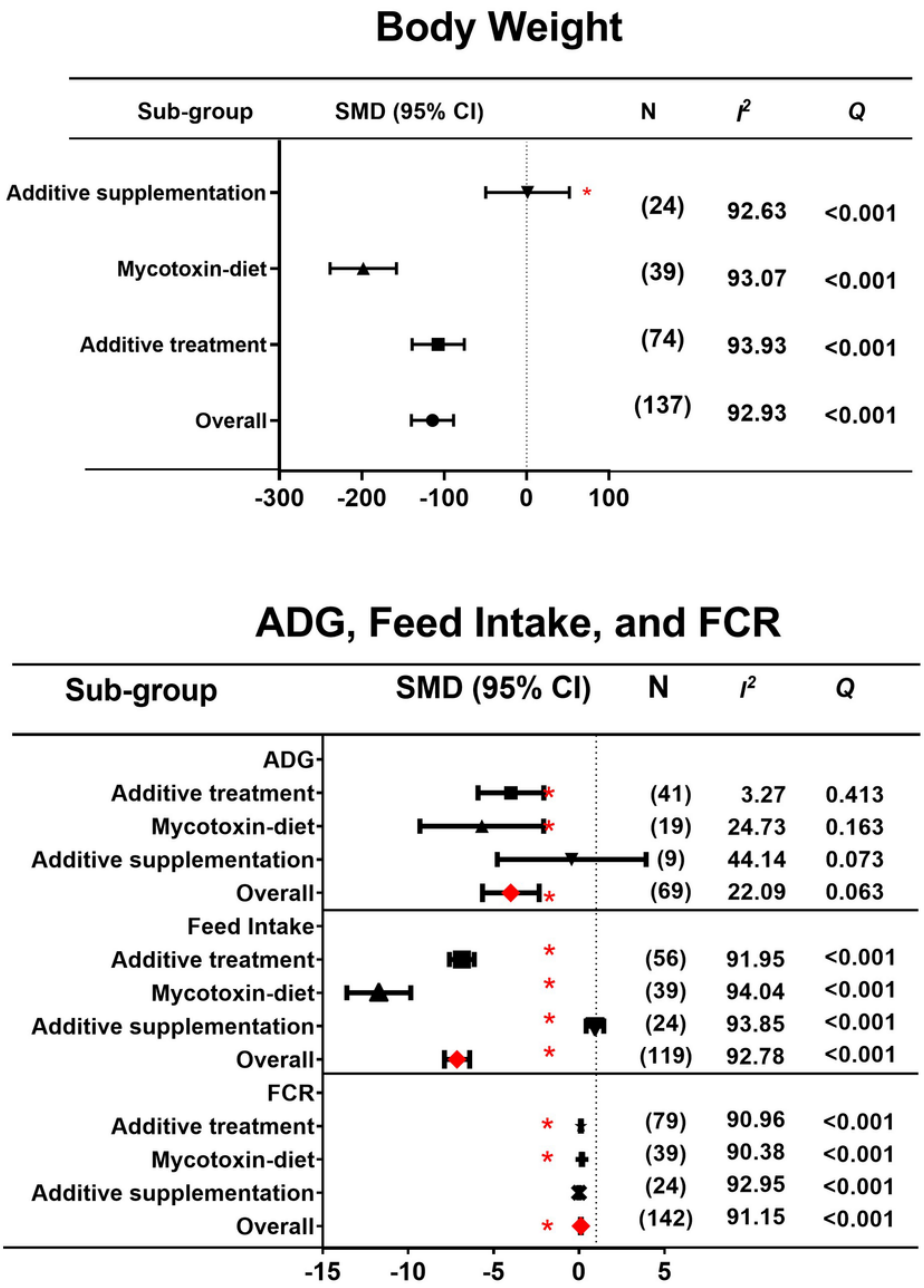

Figure 4

Forest plot of subgroup meta-analysis showing the 95% confidence intervals (lower – upper) of the standardized means difference (SMD) between the means of groups of dietary treatment (as covariates) and group of control diet. The x-axis shows the SMD; central-dashed line represents the zero effect (SMD = 0) of dietary interventions; red-diamonds represent the overall effect while the specific symbols in each line represent the SMD (subgroup effect) of the specific group. Reduction effects are reflected when the SMDs are in the left of the central dashed-line and increasing effects are in opposite (to the right of the line). Red-asterisk symbol reflects the significance of the subgroup (P<0.05). N is the sample size of specific subgroup.

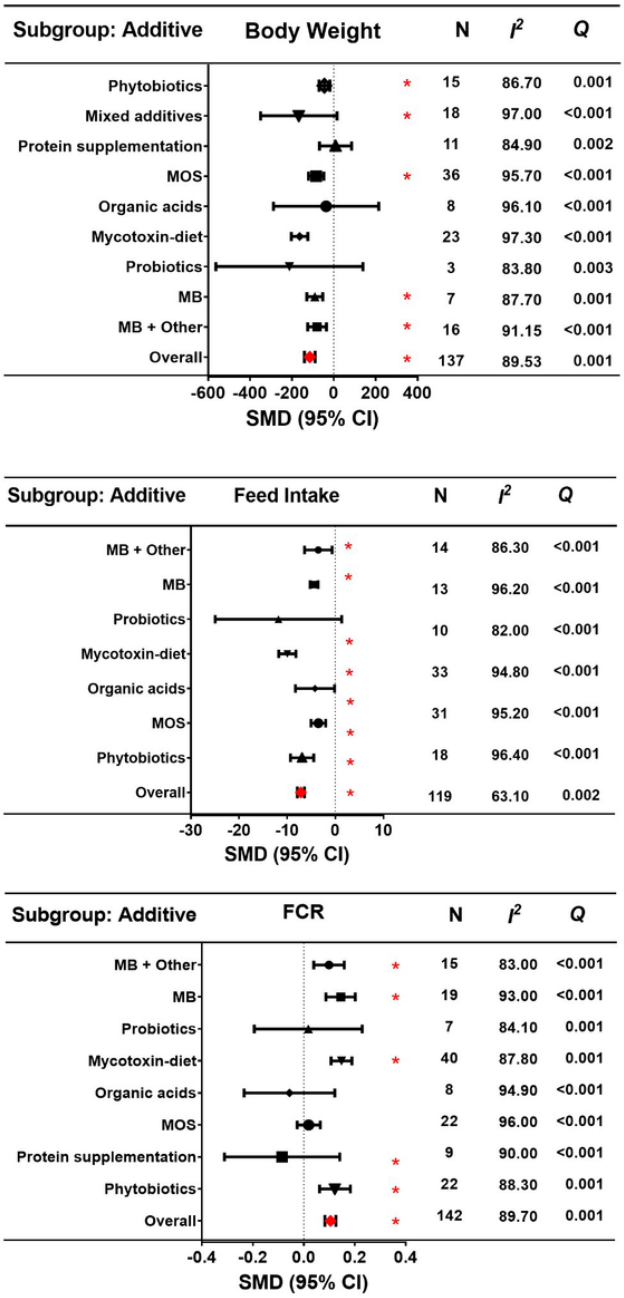

Figure 5

Forest plot of subgroup meta-analysis to evaluate the effects of different types of feed additives top-dressed onto mycotoxin-contaminated diets on body weight, feed intake, FCR. The effects are expressed at 95% confidence intervals (lower – upper) of standardized means difference (SMD) between the means of dietary interventions and group of control diet. The x-axis shows the SMD; central-dashed line represents the zero effect (SMD = 0) of dietary interventions; red-diamonds represent the overall effect while the specific symbols in each line represent the SMD (subgroup effect) of the specific group. Reduction effects are reflected when the SMDs are in the left of the central dashed-line and increasing effects are in opposite (to the right of the line). Red-asterisk symbol reflects the significance of the subgroup ($P<0.05$). N is the sample size of specific subgroup.

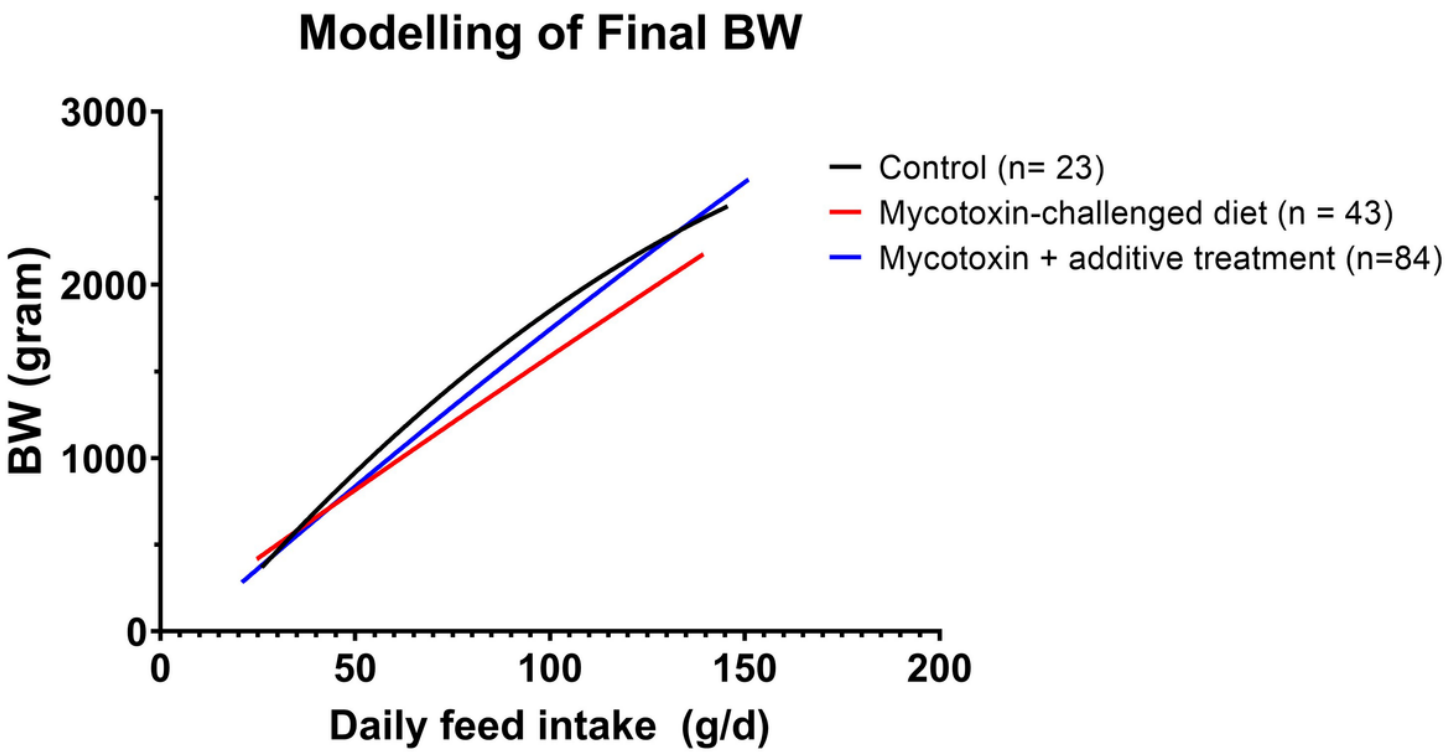

Figure 6

Modelling of the relationship between average daily feed intake as influenced by feed additives and predicted final body weight of broiler chickens. Equation: $y = -0.0567x^2 + 27.165x - 299.86$, $R^2 = 0.964$, n = 23 (control); $y = -0.0049x^2 + 16.161x + 20.183$, $R^2 = 0.978$, n = 43 (mycotoxin-challenged diet); $y = -0.0116x^2 + 19.867x - 128.34$, $R^2 = 0.984$, n = 84 (mycotoxin treated with feed additives).

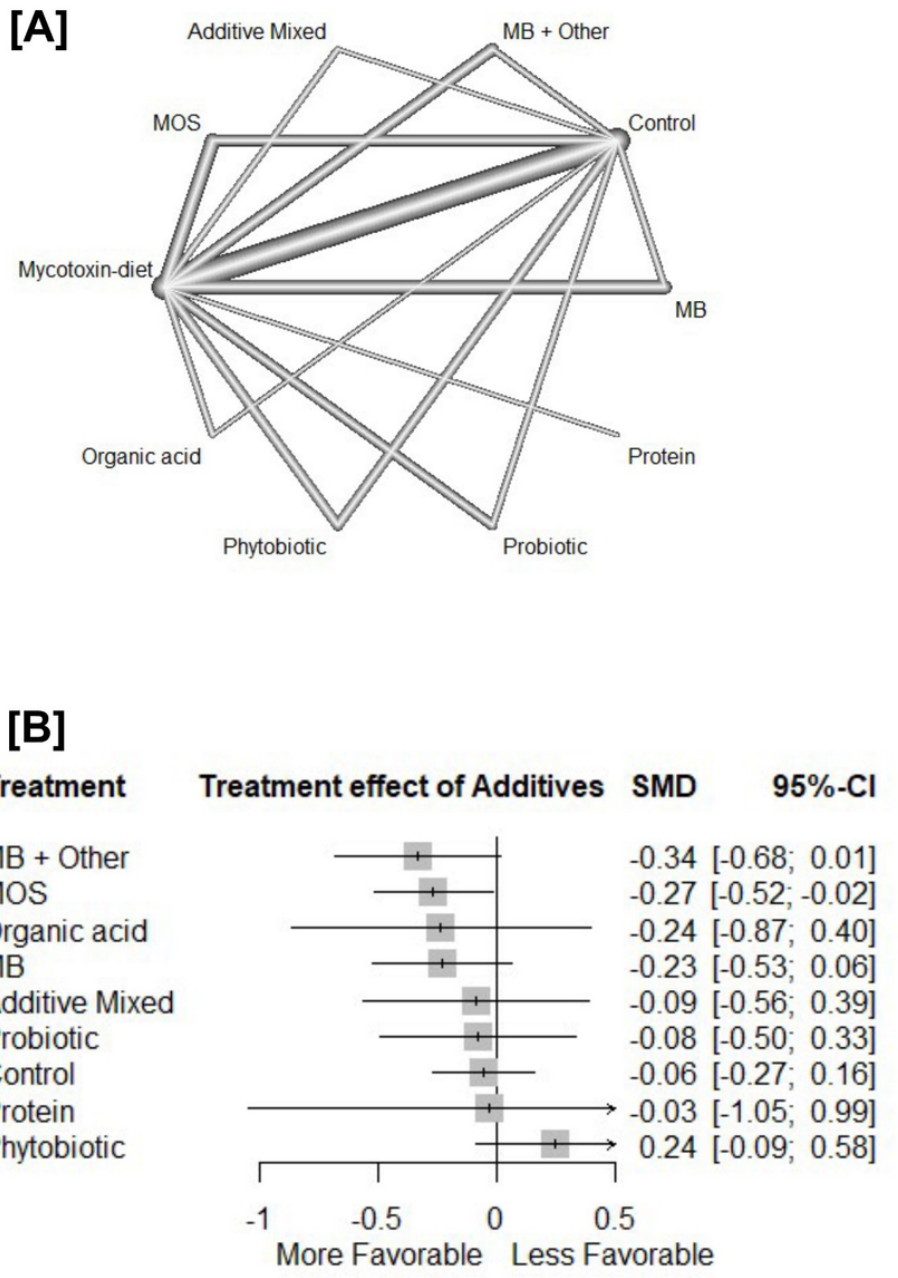

Figure 7

Structure of network comparisons used for network meta-analysis (A) and forest plot displays more favorable to less favorable feed additives as dietary interventions to ameliorate mycotoxin effects based on the effect sizes for each additive (B).

Figure 8

Heatmap plot displays the degree of inconsistency in the built network. Colored backgrounds indicate a strong inconsistency (red to blue as the highest to the lowest) and the gray background indicates the importance of the comparison (greater = more important).