



[Review Article]

A meta-analysis of Preclinical Studies About The Effect of Spray-dried Porcine Plasma on Microbiota Composition



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Abstract

MICROORGANISMS in the gut microbiota have developed alongside the host for thousands of years. Spray-dried porcine plasma (SDPP) increases development and immunity, making it a promising antibiotic replacement. In this systematic review and meta-analysis, we examined all available data on spray-dried porcine plasma's immune response and microbiota composition alterations, which may affect antibacterial effectiveness. To achieve this goal, Cochrane central, ISI web of science (WOS), PubMed/Medline, Scopus, and EMBASE were systematically searched using standard terms. No language, study region, or research kind restrictions applied. Following the exclusion criteria, this meta-analysis included 11 papers on 474 animals' important traits. Eleven studies involved 474 animals in this meta-analysis. The study involved eight pigs, three mice, one dog, bird, and fish. *Firmicutes*, *Bacteroidetes*, and other bacteria were more prevalent in SDPP-fed pig samples than in control diet samples. *Proteobacteria*, *Tenericutes*, and *Actinobacteria* were less common in SDPP-fed pig samples. SDPP did not affect growth performance measures compared to the control group. SDPP-exposed animals had higher Shannon and Simpson indices and more species, regardless of BW. In addition, treatment groups had similar colonic microbiota richness estimators (Chao 1). This study represents the first comprehensive meta-analysis to investigate the impact of SDPPs on immune response and microbiota composition alterations, which may affect antibacterial effectiveness in the peer-reviewed literature. The study's findings demonstrated that the utilization of SDPP imposes little residual effects on the overall growth performance and increases the diversity and richness of bacterial communities, ultimately leading to alterations in the microbiota composition of the animals.

Keywords: Spray-dried porcine plasma (SDPP); Intestinal health; Animal model; Meta-analysis.

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Introduction

The human gastrointestinal (GI) tract harbors a vast and intricate ecosystem of commensal microorganisms [1]. The gut microbiota, a community of microorganisms, has evolved with its host over thousands of years. It helps its host digest, produce nutrients, eliminate toxic substances, protect against diseases, and regulate the immune system [2]. The immune system is crucial for maintaining the body's overall health by effectively eliminating harmful infections while also ensuring tolerance towards beneficial self-tissue. However, in the context of individuals with autoimmune illnesses, the process of maintaining self-tolerance malfunctions, leading to the immune system erroneously targeting and eliminating healthy self-tissue. Given the intimate connection between the gut microbiota and the human immune system, it is unsurprising that specific gut microbiota components have been linked to autoimmune illnesses. Previously, the study of autoimmunity in the gut microbiota remained unclear. Still, recent advancements in "next-generation" sequencing technologies have greatly simplified the process of analysing these complex commensal communities using culture-independent microbial analysis [3-5].

The significance of microbiota in human health is becoming more and more acknowledged. The impact of gut microbiota on several conditions, such as inflammatory bowel disease, obesity, diabetic mellitus, irritable bowel syndrome, and colon cancer, has been extensively researched. Additionally, ongoing investigations are exploring its correlation with numerous other disorders [6]. Since their discovery, antibiotics have entirely transformed the way infectious diseases are treated worldwide due to the decline in mortality rates attributed to infectious diseases; they are acknowledged as one of the factors that have led to the rise in life expectancy over the 20th century [7]. Nevertheless, the excessive and incorrect utilization of antibiotics in human and veterinary medicine, as well as animal farming, has led to the present worldwide problem of antibiotic resistance. This issue is further aggravated by the sluggish pace of developing new drugs [8].

In recent years, microbial medicine has advanced significantly due to the substantial progress made in comprehending genomes, metagenomics, and metabolomics [9]. Given these advancements, manipulating the host microbiome has been suggested as a therapeutic or

preventive measure for several health conditions. The human body contains many microorganisms, with bacteria playing a significant role. Other microorganisms, including viruses, parasites, and fungi, inhabit our bodies [10]. Changes in the mutually beneficial relationship between the microbiota and the enteric microenvironment, which includes cells of the innate and acquired immune system and enteric neurons, are responsible for developing complex gut disorders such as diarrhea and chronic inflammatory bowel disease (IBD) [11, 12]. The imbalance of gut microbiota, known as gut microbiota dysbiosis, is implicated in various systemic metabolic illnesses and neurological disorders [13, 14]. Ongoing clinical trials are actively exploring the potential of next-generation therapies, which are based on microorganisms, to effectively displace or eradicate harmful microbes to cure a range of disorders in the gastrointestinal tract, skin, and vagina. These innovative treatments draw inspiration from the successful use of fecal microbiota transplants [15]. Genetically modified microorganisms are currently under investigation in clinical settings as factories for generating pharmaceuticals for biological administration. This approach has the advantage of a continuous local supply of medications. Regardless of the situation, microbe-based treatments have the potential to meet clinical needs and explore new research areas by minimizing the adverse effects of current treatment methods or by enhancing the administration of biologics. Microcapsules are crucial in safeguarding the enclosed probiotics from detrimental exterior elements, improving the viability and functionality of bacteria. Currently, extrusion, emulsification, and spray drying are well-established techniques [16]. Spray-dried porcine plasma (SDPP) is highly regarded as a potential substitute for antibiotics, as it effectively enhances growth and boosts immunity [17]. In the present systematic review and meta-analysis, we compiled and analysed every piece of data ever collected regarding the likely immunological response and microbiota composition changes resulting from spray-dried porcine plasma, which may affect antibacterial activity.

Highlights

SDPP imposes little residual effects on the overall growth performance.

SDPP increases the diversity and richness of bacterial communities.

The utilization efficiency of SDPP differs significantly.

SDPP leads to alterations in the microbiota composition of the animals.

Methods

This meta-analysis strictly followed the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [18] and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [19].

Search strategy

We extensively searched prominent indexing databases, such as Scopus, Pubmed/Medline, ISI Web of Science, Embase, Cochrane Central, and CINAHL (Table S1). The search was performed using specific keywords ((Spray[Title/Abstract]) OR (Spray-dried porcine plasma[Title/Abstract])) AND (((gut bacteria[Title/Abstract]) OR (microflora[Title/Abstract])) OR (microbiota[Title/Abstract])) OR (microbiome[Title/Abstract])), covering the period from January 1, 1980, to December 16, 2023, without any limitations on language. In addition, two prominent clinical trial registries, namely clinicaltrials.gov and the WHO clinical trials search site, were thoroughly examined. In addition, we conducted a manual search of archives containing records referenced by the previously identified articles.

Inclusion and exclusion criteria

We included studies that examined the impact of SDPP on intestinal function, oxidative state, intestinal microbiota composition, and immunologic biomarkers in animal models. If any of these conditions were not met, the article was excluded.

PICO

Population: The experimental investigation on employing SDPP includes several animal models such as pigs, piglets, mice, dogs, and rats.

Intervention: Randomly assigned two or more dietary treatments, including diet as control (no SDPP) and SDPP alone or combined with diet.

Control: A routine diet without using SDPP.

Outcome: The primary outcome of interest was an alteration of gut microbiota by exposure to SDPP or microbial populations in the ileum and cecum. The secondary outcomes were growth

performance of intrauterine growth-retarded, such as changes in body weight (BW), average daily gain (ADG), average daily feed intake (ADFI), and *G: F* ratio of ADG to ADFI. Also differences in bacterial community diversity and richness among the four treatments were compared using alpha diversity indices, including Shannon index, Chao1 index; and Simpson index [20].

Study selection

Data from several experiments were included as different entries under the same publication reference whenever results from multiple studies were reported in the same publication. Each research was considered an independent experiment. Two writers, FR and LD, independently checked studies to see if they met the inclusion criteria. In the event of a disagreement, the writers would seek advice from a third party or refer back to the referenced book (KD)..

Methodological quality assessment

Two authors, FR and LD, independently reviewed the validity of the methodology, giving particular attention to the potential sources of bias. In order to evaluate the scope of the potential for bias in randomized controlled trials (RCTs), we utilized the quality assessment instrument developed by the Cochrane Collaboration[21]. In the event that there was a disagreement, it was resolved by either carefully verifying the reference article or consulting with a third author (KD).

Data extraction

We used the RevMan 5.3 software to examine the data and applied the standardised mean difference as the effect size. We employed the methodologies established by Wan *et al.* [22] to calculate the average and variability of the data when it was provided as a median value and a range. The phrase “total variability” (*I*²) was employed to denote heterogeneity. The hypothesis of substantial heterogeneity was assessed using the χ^2 test. A heterogeneity level was considered modest when the *I*² score was below 40%. Before the meta-analysis, the cause of heterogeneity was determined if the heterogeneity was deemed significant (*P* greater than 75%). We conducted sub-group analyses using various comparators. We employed funnel plots to assess the presence of publication bias. Significance was determined by p-values lower than 0.05.

Results

Description of the included studies

Out of the 544 total founded studies, 175 were detected during the initial searches, with just 13 meeting the inclusion criteria for quantitative synthesis (Figure 1). This meta-analysis contained eleven publications, which involved a total of four hundred and seventy-four animals. The animals included in the study were eight pigs, three mice, and one each of dogs, birds, and fish. The inclusion of these papers was based on the application of specific exclusion criteria (Table 1).

Quality of the evidence

Fig.S1 provides a comprehensive summary of the bias risk associated with each individual study. For all the investigations, it was not possible to obtain information about blinding, resulting in a determination of a high risk of bias. Randomization and allocation concealment were deemed appropriate in all 12 research, resulting in a low risk of bias.

Alteration of gut microbiota

The prevalence of phylum *Firmicutes*, *Bacteroidetes*, and other bacteria was considerably more significant in the samples from pigs that were given the SDPP diet than those given the control diet (Table 2). Conversely, the prevalence of *Proteobacteria*, *Tenericutes*, and *Actinobacteria* was lower in the samples from pigs fed the SDPP diet. Bacteria mentioned in fewer than three research were documented in Table S2_(Supplementary file).

Growth performance

Most of the studies were reported the indices showing growth performance in response to using SDPP. There was no significant change in growth performance indices following the use of SDPP compared to the control group (Fig. 2).

Differences in bacterial community diversity and richness among the four treatments

Regardless of BW, the Shannon index and Simpson index of samples from animals exposed to SDPP showed significant increase, and the observed species of these samples tended to increase (Figure 3). In addition, no remarkable differences were observed in the richness estimator (Chao 1) of the colonic microbiota among treatment groups (Fig. 3).

Analysing the Impact of Publication Bias and Variables

The meta-analysis included a total of 11

publications. The approaches that Begg and Egger's empirical research created were utilized to evaluate the presence of publication bias. Additionally, a visual evaluation of funnel plots for symmetry was considered necessary (Fig. 4). The statistical tests revealed a low probability of editorial bias ($p > 0.05$). To assess the strength and reliability of the findings, the eleven publications included in the meta-analysis underwent a sensitivity analysis. Even after excluding individual research articles, there was minimal variation in the overall impact magnitude, which also substantiates the credibility of the findings from this meta-analysis.

Discussion

Studies utilizing SDPP have reported multiple production enhancements. The improvements consist of higher voluntary feed intake during lactation for sows in their first and second reproductive cycles, a shorter time between weaning and the first estrus for sows in their first reproductive cycle [36], a higher rate of successful subsequent farrowing [37], improved survival rates before weaning [38, 39], increased litter weight, and higher average pig weight at weaning [36], resulting in a more significant number of high-quality piglets weaned per litter. To our knowledge this study represents the first comprehensive meta-analysis to investigate the impact of SDPP on immune response and microbiota composition alterations, which may affect antibacterial effectiveness in the peer-reviewed literature. The study's findings demonstrated that the utilization of SDPP imposes little residual effects on the overall growth performance and increases the diversity and richness of bacterial communities, ultimately leading to alterations in the microbiota composition of the animals.

The prediction in this meta-analysis about functional profiling of the bacterial communities revealed that bacteria associated with metabolic processes, such as starch, sucrose, and amino acid metabolism, were more abundant in pigs fed the SDPP diet. Prior research has demonstrated that enhancements in the amino acid metabolism pathway levels are regarded as a reliable predictor of more efficient utilization of dietary protein [40, 41]. One of the prevalent bacteria affected by SDPP was *Firmicutes*. The human gut microbiome comprises many species, predominantly bacteria. *Firmicutes* are particularly favored by scientists due to their significant role in preserving metabolic and

immunological well-being [42, 43]. Researchers have identified more than 200 distinct bacterial species that are classified inside the *Firmicutes* phylum. This article presents significant species of *Firmicutes*, their role in promoting gut health, and dietary recommendations to support their growth. Another group significantly impacted by SDPP is *Bacteroidetes*, which constitute approximately 50% of the microbiota and colonize the whole gastrointestinal tract, including the mouth cavity and stomach. Metabolizing polysaccharides and oligosaccharides, *Bacteroides* not only nourishes the host and other microbes in the gut, but it also protects them from harmful infections and gives them nutrients [44].

Our meta-analysis showed that animals exposed to SDPP had higher final BW, ADG, and F/G, which suggests that SDPP may positively affect the growth performance of animals. However, when we analysed the data from multiple studies, we found no significant difference in growth performance between the SDPP and the control groups. Che *et al.* [45] also reported no significant differences on growth performance between the SDPP and control diets.

Our present meta-analysis shows that animals exposed to SDPP had significantly higher microbial diversity, as measured by Shannon and Simpson indices. Many researchers believe inflammatory bowel disorders (IBD) and other infectious bowel diseases are linked to low microbial diversity [46]. Galazzo *et al.* [47] investigated the composition of the gut bacteria in adult patients with Crohn's disease [CD] who experienced either altering or stable disease progression over time. The study revealed that a fraction of CD patients had an abnormal composition of gut bacteria, suggesting that further research is needed to explore the role of gut bacteria in developing this disease. The underlying cause of IBD is a deficient immune response to microorganisms in the gastrointestinal system. IBD has a partially heritable risk, with around 12% of individuals having a familial history of the condition [48]. IBD was connected with 240 genomic areas through extensive genome-wide association studies (GWAS). Many genes involved have a role in the immune system and are linked to primary immunodeficiency or the body's defence against mycobacteria [49]. Thus, the improvement in animal intestinal health observed in the SDPP group compared to the control group throughout the experiment is attributable to the enhanced microbial diversity that this diet

promotes. Our meta-analysis also confirms shifts in alpha bacterial diversity in SDPP-exposed animals' colons, as assessed by the Chao 1 index, which measures bacterial community richness. The results of our meta-analysis align with prior studies that have documented a higher abundance and variety of microorganisms in pigs who were given SDPP and exposed to *E. coli* K88 [50].

Conclusion

The utilization of SDPP with functional blends containing probiotics may potentially result in positive impacts on stool quality, fecal metabolites, and immune function. These specific blends enhance the prevalence of distinct essential bacterial genera, hence positively altering the gut microbiota. In future investigations, researchers should explore the utilization of shotgun sequencing as a means to examine the functional capacity of the microbiota or consider alternate methodologies that may yield more precise and reliable measurements of SDPP production. This work represents the inaugural investigation into the impact of SDPP on immune response and alterations in microbiota composition, which could affect the effectiveness of antibacterial agents. The findings indicated that the utilization of SDPP did not have any enduring impact on the overall growth performance of the animals. However, it does enhance the diversity and quantity of bacterial populations, hence altering the animals' microbiota. Potential areas for future research are investigating the effects of these combinations of fiber, probiotics, and immunomodulating substances on animal populations that are prone to inflammatory conditions and disruptions in gut microbial balance.

Ethical Considerations

Compliance with ethical guidelines
NA.

Funding statements

Authors received no fund.

Authors' contributions

FR: Developed the concept, conducted the data analysis, wrote, and revised the first draft of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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NA

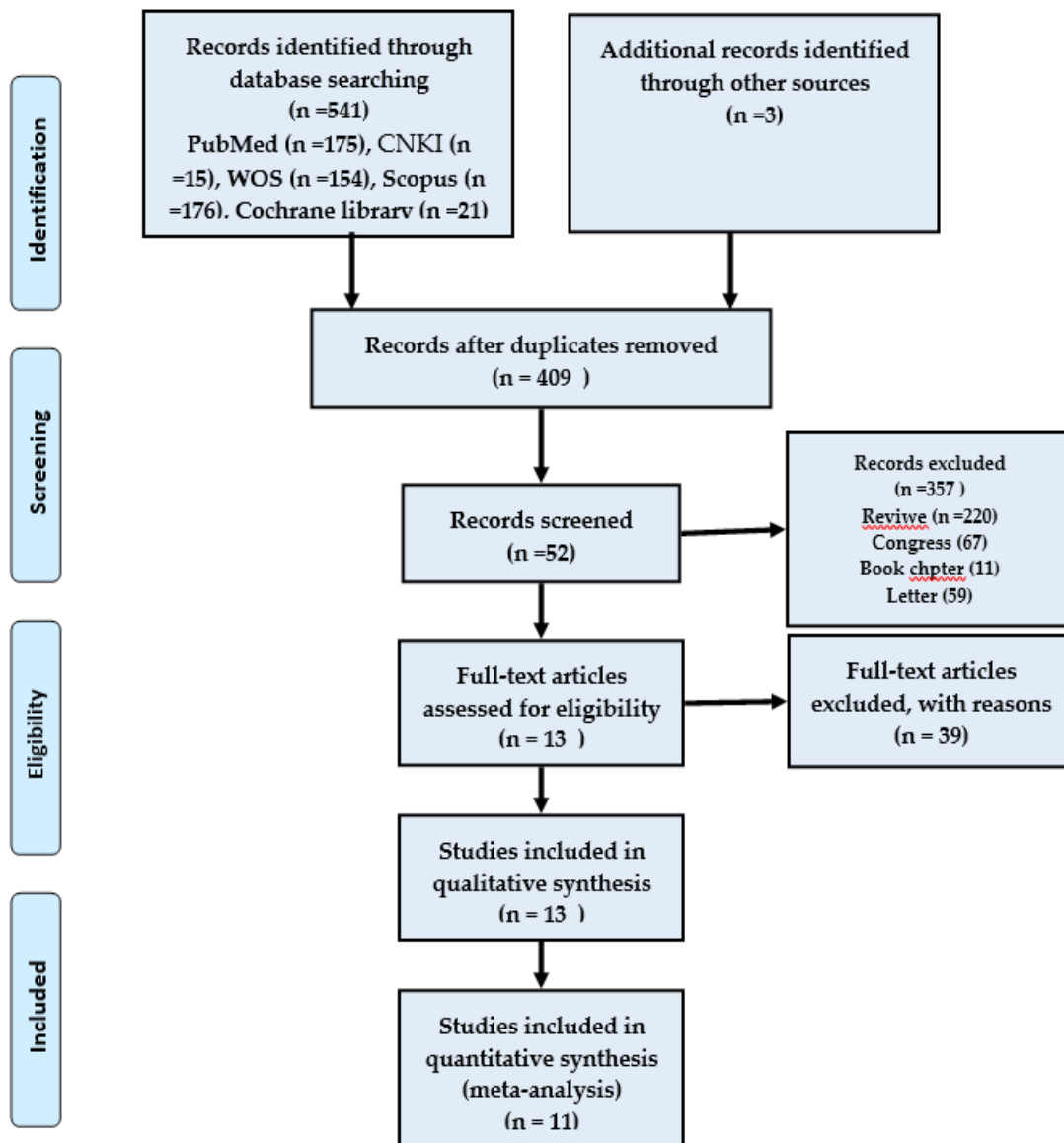


Fig. 1. PRISMA flow diagram of included studies.

TABLE 1. Basic characteristics of the included studies.

Study ID, reference	Number of cases	Target group	Study groups	Spray %	Treatment duration	Variables	Bacterial change
Zhang <i>et al.</i> 2023 [23]	24	Landrace/Yorkshire crossbred piglets	G1: CTL G2: SDPP	6%	18 days	<i>IL-6</i> and <i>IL-10</i> ↓	Higher <i>Marinifilaceae</i> , <i>Fisobacterium</i> and <i>Enterococcus</i>
Daneshmand <i>et al.</i> 2023 [24]	30	Male broiler parental line chicks (Ross 308)	G1: CTL G2: SDPP	2%	28 days	<i>IL-6</i> , <i>IgA</i> , <i>IgG</i> and <i>IL-10</i> ↓ <i>IgM</i> ↑	-----
Rosell-Cardona <i>et al.</i> 2022 [25]	27	Male SAMMP8 mice	G1: CTL G2: SDPP	8%	120 days	<i>Thr2</i> , <i>Thr4</i> and <i>Thr9</i> , genes <i>Muc2</i> and <i>Tff3</i> ↑ <i>IL-10</i> and <i>Tgf-β</i> ↑	Increase <i>Lactobacillus</i> and <i>Pediococcus</i> , while reducing the abundance of inflammation-associated bacteria, such as <i>Johnsonella</i> and <i>Erysipelothrix</i> . Spray increased Firmicutes, which increased lactobacilli, regulatory T-lymphocyte homeostasis species, mucosal barrier restoration, and species inversely linked with pro-inflammatory cytokines.
Lee <i>et al.</i> 2022 [26]	12	healthy adult intact English pointer dogs	G1: CTL G2: SDPP	8%	28 days	<i>TNF-α</i> ↓	Decreased Bacteroidetes, increased Firmicutes, <i>Lactobacillus</i> , and <i>Streptococcus</i>
Zh <i>et al.</i> 2021 [27]	192	Healthy weaning piglets	G1: NCTL G2: PCOL G3: SDPP	5%	14 days	-----	-----
Crenshaw <i>et al.</i> 2021 [28]	452	Natima Choice Genetics pigs	G1: CTL G2: SDPP	5%	14 days	<i>IFN-α</i> , <i>IL1β</i> , <i>IL-4</i> , <i>IL-6</i> ↓ <i>IL-10</i> , <i>IL-8</i> , <i>TNF-α</i> , <i>IL-12</i> ↑	-----
Che <i>et al.</i> 2020 [29]	36	normal birth weight weaned pigs	G1: CTL G2: SDPP	8%	14 days	-----	Spray improved bacterial diversity and increased the abundance of phylum Firmicutes, but decreased the phylum Proteobacteria in colonic digesta, associating with higher genera <i>Lactobacillus</i> and lower genera <i>Escherichia-Shigella</i> . Spray increased Firmicutes, which increased lactobacilli, regulatory T-lymphocyte homeostasis species, mucosal barrier restoration, and species inversely linked with pro-inflammatory cytokines.
Moretó <i>et al.</i> 2020 [30]	18	Weaned 21-day-old C57BL/6 mice	G1: CTL G2: COL G3: SDPP	8%	14 days	<i>Thr2</i> , <i>Thr4</i> and <i>Thr9</i> , genes <i>Muc2</i> and <i>Tff3</i> ↑ <i>IL-10</i> and <i>Tgf-β</i> ↑	Lower concentration of <i>Escherichia-Shigella</i> and <i>Campylobacter</i>
Silva Júnior <i>et al.</i> 2020 [31]	108	crossbred piglets	G1: NCTL G2: PCOL G3: SDPP G4: SDCP	--	65 days	-----	<i>Clostridiaceae</i> increased on day 14, but decreased on day 28
Tran <i>et al.</i> 2018 [32]	96	weaned pigs	G1: CTL G2: SDPP	5%	28 days	-----	Decreased <i>Veillonellaceae</i> on day 14 and <i>Lachnospiraceae</i> overall. Decreased the populations of <i>E. coli</i> . The population of <i>Lactobacillus</i> increased
Zhang <i>et al.</i> 2015 [33]	144	normal birth weight weaned pigs	G1: NCTL G2: PCOL G3: SDPP G4: SDCP	5%	28 days	-----	-----
Gisbert <i>et al.</i> 2015 [34]	40	Gilt head sea bream fry	G1: CTL G2: SDPP	6%	14 days	Nonspecific immune responses↑	-----
van Dijk, 2002 [35]	68	normal birth weight piglets	G1: CTL G2: SDPP	5%	14 days	-----	influencing the gastrointestinal microflora

G, group; CTL, control diet; COL, low doses of neomycin and colistin; SDPP, spray-dried porcine plasma; NCTL, negative basal diet; PCOL, positive control; SDCP, spray-dried chicken plasma protei

TABLE 2. The alteration of gut microbiota in response to SDPP

Gut microbiota	No. of trials	No. of participants	SMD	95% CI	<i>p</i>	<i>I</i> ² (%)	<i>p</i> for heterogeneity
<i>Firmicutes</i>	5	91	2.64	0.34, 4.94	0.02	93%	<0.00001
<i>Proteobacteria</i>	4	79	-0.32	-3.43, 2.79	0.84	95%	<0.00001
<i>Bacteroidetes</i>	6	112	1.59	0.18, 3.00	0.03	89%	<0.00001
<i>Tenericutes</i>	3	61	-0.49	-1.68, 0.71	0.43	79%	0.008
<i>Actinobacteria</i>	4	67	-5.95	-10.17,-1.73	0.006	94%	<0.00001
<i>Other</i>	6	112	1.41	-0.12, 2.95	0.07	90%	<0.00001

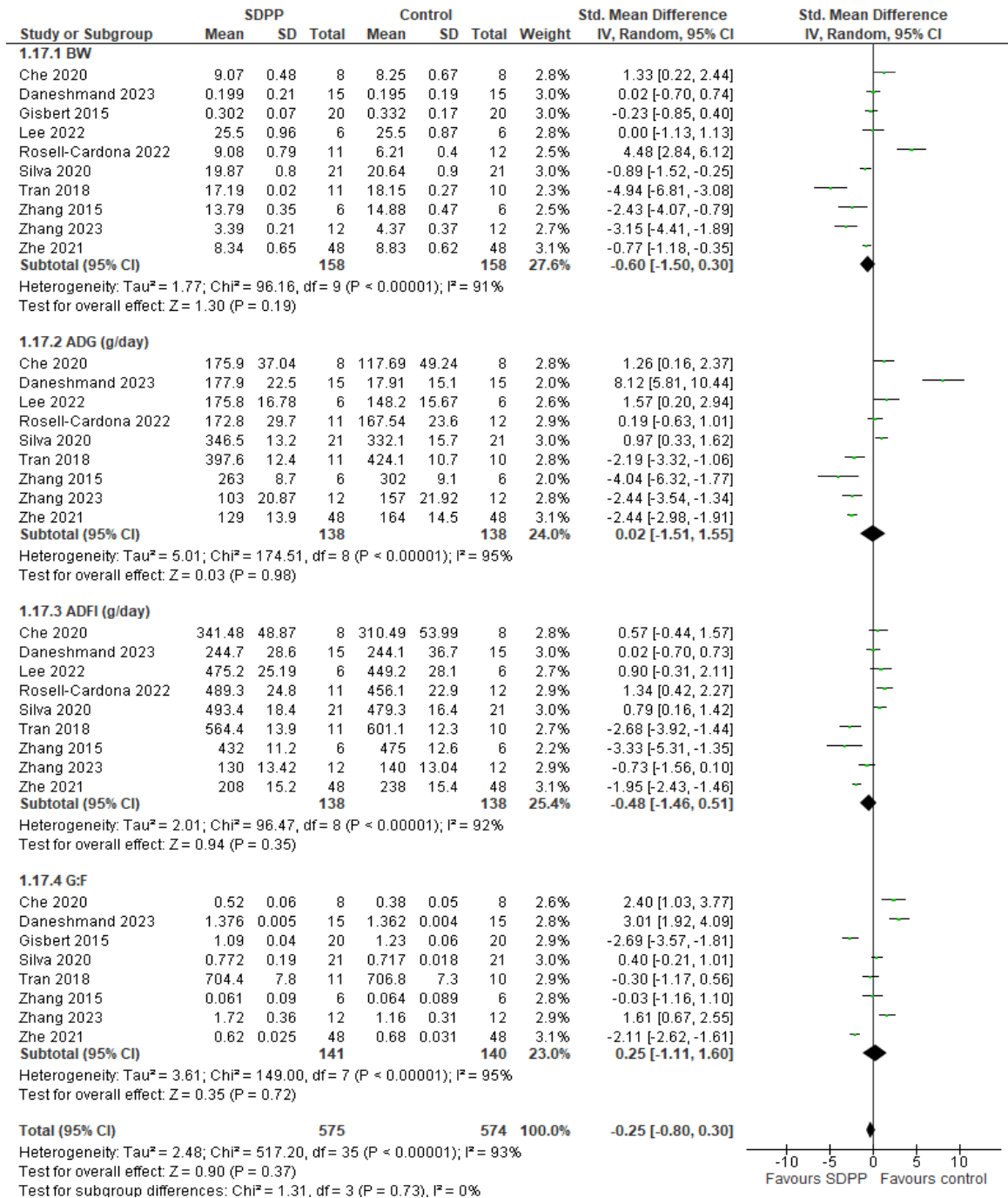


Fig. 2. Forrest plot of comparing different indices to show the effect of SDPP on animal growth performance

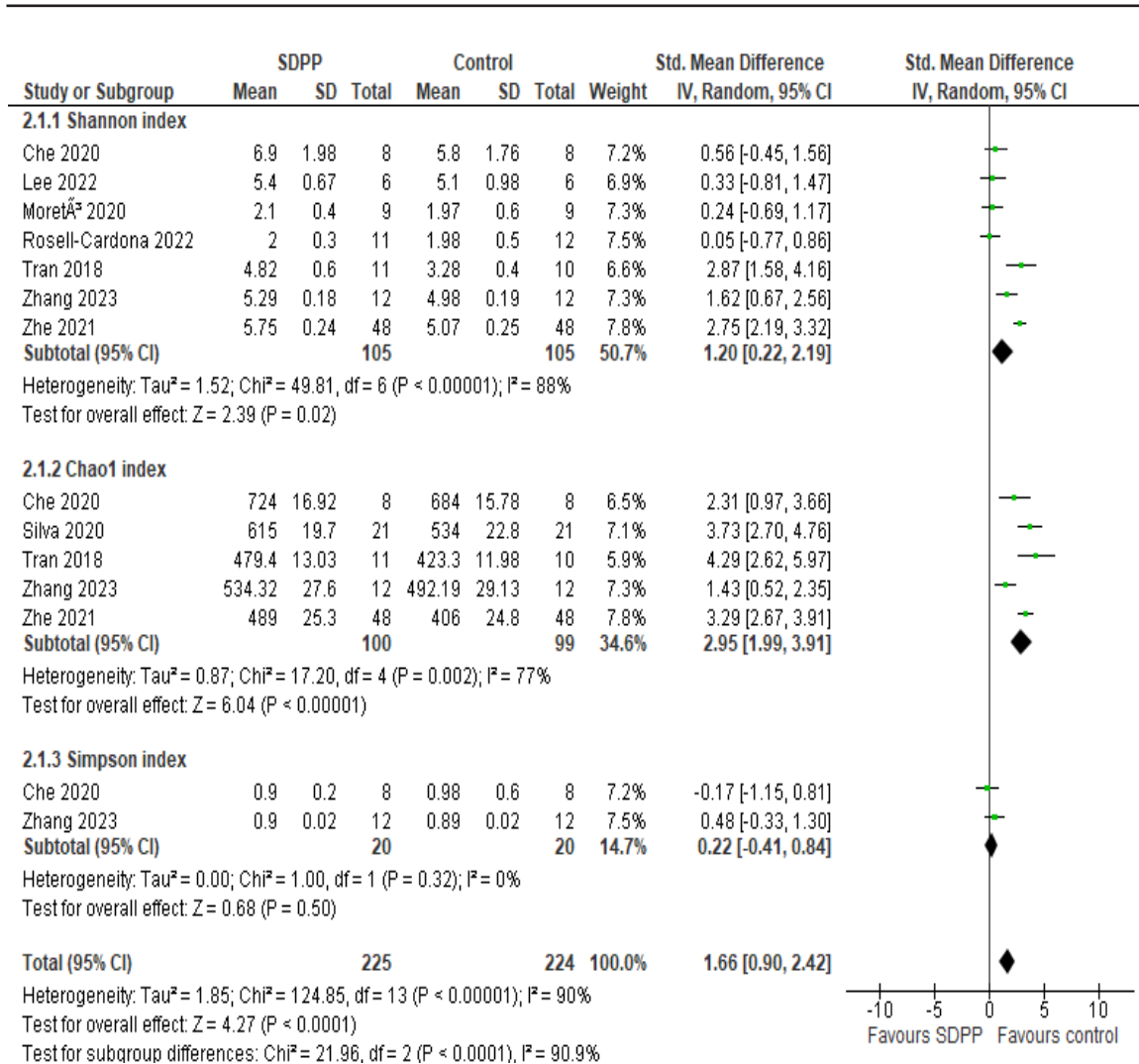


Fig. 3. Forrest plot of comparing the differences in bacterial community diversity and richness among animals using SDPP

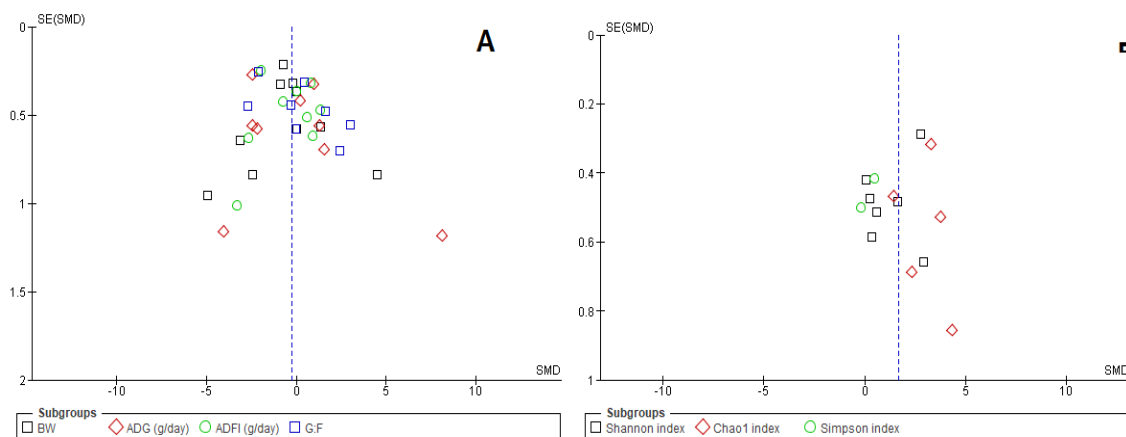


Fig. 4. Funnel plots of growth performance due to alteration of microbiota (A), bacterial community diversity and richness (B) in response to SDPP

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