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Review

Immune Response to Spray-Dried Porcine Plasma-Fed Diet: A Systematic Review and Meta-Analysis of Animal Model

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Abstract: Spray-dried plasma (SDP), a byproduct of the meatpacking industry, is commonly used in swine diets to enhance growth and optimize feed utilization. Multiple studies have shown that animals' immune responses can be improved by giving them plasma proteins like SDP orally. This study aims to highlight the importance of non-invasive dietary interventions in stimulating immune responses and enhancing immunological characteristics. A comprehensive search was conducted using the indexing databases Scopus, PubMed/Medline, ISI Web of Science, Embase, Cochrane Central, and CINAHL and out of the 541 publications initially searched, only 13 fit the specified criteria. This meta-analysis incorporated seven trials, including a total of 210 animals. The SDP group had significantly lower IL-10 levels (SMD: −1.79, 95% CI: −2.43, −1.15, I2: 60%, $p = 0.04$) compared to the control group. The SDP group showed statistically higher TNF-α (SMD: 2.32, 95% CI: 0.74, 3.89, I^2: 92%, $p = 0.004$) than the control group. Also, the SDP group showed statistically higher IgG (SMD: 0.59, 95% CI: 0.03, 1.15, I^2: 54%, $p = 0.04$) than the control group. SDP alters cytokine secretion, promoting an anti-inflammatory immune profile. The positive impact of SDP in this model suggests that these supplements may help enhance immune responses.

Keywords: Spray-Dried Porcine Plasma (SDPP); Intestinal Health; Animal Model; Meta-Analysis; Cytokines

1. Introduction

1.1. Background and Aims

Spray-dried plasma (SDP) is a residual substance derived from the meatpacking industry and is commonly used in swine diets to enhance development and optimize feed utilization [1]. SDP can undergo additional processing to standardize the concentration of immunoglobulins. This procedure enables easier manipulation of the product within the manufacturing facility or transforms it into a product that can dissolve in water [2]. Research has linked this product's action to specific nucleotides and immune-reactive globulins in blood products [3].

The composition of gut microbiota might vary considerably among individuals. Nevertheless, numerous indispensable bacterial species are frequently present in most instances. Diet is considered to significantly impact the structural variances of microbes in mice, contributing to almost 50% of these changes. The influence of food is projected to account for 20% of the observed differences in humans, suggesting that dietary interventions could be used to manage diseases by modifying the gut microbiota [4,5].

A growing body of evidence showed that adding SDP to broiler chickens' diet from day 0 to day eight enhanced immunological homeostasis, as evidenced by reduced cytokines and immune-related proteins. Multiple studies have shown that animals' immune responses can be improved by giving them plasma proteins like SDP orally. These studies have focused on various mechanisms [6], such as raising Ig levels, boosting the overall immune response, modulating the function of immunocompetent cells [7,8], increasing the number of lymphocytes, making them more active phagocytes, and increasing the concentration of antibodies in the gut [9]. Experiments on rats exposed to *Staphylococcus aureus* toxin (SAT) have shown that SDP influences their immunological response. Researchers showed that SDP could affect immune system function by blocking SAT-induced activation of CD4 T-helper cells, reducing SAT's influence on pro-inflammatory cytokine release, and enhancing IL-10 production in the intestinal mucosal layer [10,11]. A further study found that SDP reduced the production of salivary IgA and the expression of pro-inflammatory cytokines in the gastrointestinal tract of young piglets who were weaned early and exposed to *E. coli K88* [12]. Additional studies have shown that administering immunoglobulins orally decreases the activation of T-helper lymphocytes (Th1 and Th2) and cytokines (IFN-γ, IL-5, IL-12, IL-13, and IL-17) by *E. coli* in the blood and lungs. Furthermore, it increases a mouse model's gene expression and concentration of the anti-inflammatory cytokine IL-10 [13]. Prior studies demonstrated that supplementation of SDP reduced IL-6 levels in rats and pigs compared to groups subjected to a challenge [14,15].

Previous research [16] has shown that dietary SDP increased the number of intestinal goblet cells without causing significant changes to the autochthonous microbiota. However, there is insufficient knowledge regarding the specific processes in the digestive system of gilthead sea bream when fed a diet containing SDP. This study aims to showcase the importance of utilizing non-invasive dietary intervention to stimulate immune response and enhance immunological characteristics.

1.2. The Role of Nutrition in the Immune System

The immune system is a collection of cells and organs that protect the body from disease and, in the event of illness, restore health [17,18]. The main function of the immune system is to destroy pathogens such as bacteria, viruses, and parasites. Another role of the immune system is to destroy damaged or abnormal cells. Most of the time, the immune system works invisibly, but sometimes when it encounters pathogens, it becomes clearly and noticeably active. For example, fever, headache, sore throat, and muscle aches are symptoms of the flu, which is caused by a virus and may affect a person for several weeks, and the immune system must fight against it. The immune system is a type of defense mechanism in the body that enables the body to resist pathogens and eliminate these harmful agents by producing a variety of cells and defense molecules. In order for the immune system to perform its functions optimally, it must be strengthened in various ways. One way to strengthen the immune system is to consume nutritious foods. The foods we eat have an effect on the immune system through the nutrients they contain, including vitamins, minerals, and fiber. Here, we will explain the role of several types of these nutrients in strengthening the immune system.

One of the important factors affecting the functioning of the immune system is nutrition, as malnutrition reduces the body's immune activity and, as a result, the occurrence of diseases, and creates a feedback loop in which the resulting disease reduces food intake and, as a result, worsens the nutritional status [19]. It should be noted that energy is provided in accordance with the individual's needs [20]. In general, energy is provided through carbohydrates, proteins, and fats found in food. The principle of balance should be observed in carbohydrate consumption because both low and high carbohydrate intake reduces the activity of the immune system [21].

Protein intake should also be paid attention to because reducing its consumption reduces the activity of the immune system. Excessive fat consumption has a negative effect on the functioning of the immune system. It is better to consume omega-3 food sources (soybean oil, canola oil, fish oil) because this type of fatty acid enhances immunity and has anti-inflammatory properties [22]. Vitamins A, D, E, B, C, zinc, and selenium play a role in the activity of lymphocytes, the production of antibodies, and the regulation of the immune system, so consuming their food sources or supplementing these vitamins should be considered to strengthen the immune system [23]. The amino acid arginine also plays a role in strengthening this system by directly affecting the proliferation of immune system cells. Various studies indicate that probiotics also play a role in strengthening the immune system [24]. As has been observed, a balanced and varied diet will have a significant impact on the functioning of the immune system, and a deficiency in any nutrient will disrupt the functioning of the immune system [25].

1.3. Dietary Intervention and the Immune System

Immunity is ensured by a diet containing meat, dairy products, fruits and vegetables, and nuts, because all macronutrients and micronutrients play important roles in the immune system. A high-fiber diet, including fruits, vegetables, whole grains, and legumes, can help maintain and enhance the health of your gut bacteria. By fermenting the fiber, the gut bacteria produce short-chain fatty acids, which, in addition to their anti-inflammatory properties, help stimulate immune cell activity [26]. Studies have shown that these beneficial compounds help to keep your digestive system functioning properly and eliminate waste and toxins [27].

Beneficial microorganisms in the digestive tract are called probiotics. Fiber, which is a kind of food for probiotics, is called prebiotics and helps maintain and increase their colonies in the digestive tract. Prebiotics are provided by consuming sources containing fiber. Probiotics, or beneficial bacteria, reach the digestive tract through the consumption of fermented food sources and settle there [28]. Foods containing prebiotics (fiber) and probiotics (beneficial microorganisms) are included in the group of functional foods. Functional foods are foods that, in addition to nutritional value, also have health-promoting properties. Consuming these types of functional foods has numerous health benefits in the body, including improving the body's immune system, compensating for antibiotic damage to the body, and reducing inflammation [29].

Essential fatty acids, called omega-3 and omega-6 fatty acids, have immune system-regulating functions and play a role in the body's inflammatory response. Alpha-linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid are unsaturated fatty acids of the omega-3 family. Alpha-linoleic acid is found in nuts and seeds, while the other two fatty acids are fish oil. It is worth noting that these two fatty acids can also be synthesized from food sources containing alpha-linoleic acid. A proper diet that contains a variety of fish, seeds, and nuts can provide the omega-3s our body needs. In general, sources of omega-3 include flaxseed, soybeans, corn seeds, chia seeds, hemp seeds, purslane seeds, walnuts, broccoli, and various types of fish [30].

Some phytochemicals (plant nutrients) have been shown to help boost the immune system. For example, garlic's immune-boosting properties come from its high concentration of sulphur-containing compounds. They can activate germ-fighting T-lymphocytes and help the immune system fight off infection. Ginger is another one that many people turn to after getting sick. It has antioxidant properties and anti-inflammatory potential due to a compound called gingerol. Ginger helps reduce sore throats, treat infections, and treat inflammatory diseases [31]. Research has also shown that glucosinolates, bioactive compounds found in turnips, have immune-boosting properties, help flush carcinogens from the body, and prevent DNA damage and subsequent cell damage that can lead to tumor growth [32].

1.4. Nutritional Intervention and Immune Repose

Food security and food safety are different but related concepts that have a profound impact on the quality of human life. Safe, uncontaminated food is essential for human health and life (food safety). Many people around the world do not have access to food or the financial means to buy enough and appropriate food (food insecurity). Access to sufficient quantities of safe and nutritious food is key to sustaining life and promoting health [33]. Unsafe food containing harmful bacteria, viruses, parasites, or chemicals causes more than 200 diseases ranging from diarrhea to cancer. This also creates a vicious cycle of disease and malnutrition, which particularly affects infants, children, young children, the elderly, and the sick. Food intolerance and food allergies are two conditions that cause similar side effects but affect the body in different ways. The immune system attacks and neutralizes foreign invaders that are potentially dangerous to the body. However, in some cases, due to certain genetic changes, the immune system attacks harmless substances, such as certain foods, called food allergy [34]. This reaction usually occurs moments after eating the food, and even a small amount of it can cause symptoms. A common example is shortness of breath and low blood pressure after contact with peanuts or seafood. It is important to seek immediate medical attention for food allergies, and treatment plans may include medication or the use of an epinephrine auto-injector. In general, common food allergens include peanuts, tree nuts, shellfish, fish, milk, eggs, and soy. Food intolerances, unlike food allergies, which are triggered by the immune system, have their roots in the digestive tract. Food intolerances are generally more severe than allergies [35]. However, symptoms can be managed by avoiding the offending foods or taking medication.

1.5. Allergic Response to Animal-Derived Drugs

In general, pet allergies happen once a person's immune system overreacts to a substance in their animal's body. In some cases, these allergic reactions can be caused by animal products. More specifically, the immune system produces antibodies to protect against infections and unwanted invaders when exposed to allergens. When allergens enter the body, the immune system mounts an inflammatory response in the airways. In some cases, prolonged exposure to allergens can cause persistent inflammation of the airways, causing problems for the individual. Treatments are available that allow people who have had allergic reactions to receive such products. People who have had repeated and severe allergic reactions to plasma may need to receive washed red blood cells. Washing the red blood cells removes components of the donated blood that may cause allergic reactions. Because white blood cells and platelets are filtered out of the donated blood before it is stored (a process called leukocyte depletion), allergic reactions are now less common.

2. Methods

The meta-analysis adhered rigorously to the PRISMA and MOOSE guidelines [36,37].

2.1. Search Strategy

The Scopus, PubMed/Medline, ISI Web of Science, Embase, Cochrane Central, and CINAHL indexing databases were thoroughly examined (**Table 1**). The search was performed using precise 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]) AND (immunological response[Title/Abstract]) from January 1, 1980, to February 16, 2025 (**Table 1**). Additionally, the Clinicaltrials.gov and the WHO clinical trials search site were assessed.

Table 1. Search terms and hits.

Search	Query	Results
#1	"Microbiome"[Title/Abstract]	59,603
#2	"Microbiota"[Title/Abstract]	97,792
#3	"Microflora"[Title/Abstract]	18,742
#4	"Gut bacteria" [Title/Abstract]	4,649
#5	(((gut bacteria[Title/Abstract]) OR (microflora[Title/Abstract])) OR (microbiota[Title/Abstract])) OR (microbiome[Title/Abstract])	144,400
#6	"Spray"[Title/Abstract]	33,814
#5 and #6	(Spray[Title/Abstract]) AND ((((gut bacteria[Title/Abstract]) OR (microflora[Title/Abstract])) OR (microbiota[Title/Abstract])) OR (microbiome[Title/Abstract]))	175
CNKI	("Spray" OR "Spray-dried porcine plasma") AND ("gut bacteria" OR "microflora" OR "microbiota" OR "microbiome")	15
PubMed	((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]))	175
Web of Science	("microbiota" OR "microbiome" OR "microflora" OR "probiotic" OR "probiotics") AND ("Spray-dried porcine plasma"). Then, use its built-in filtering function in web of science to filter out studies with study types "Abstract", "Meeting", "News", "Letter", "Biography", "Book", "Correction", "Unspecified" , "Editorial Material", "Case Report", "Early Acess", "Other", "Review Article"	154
Scopus	((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]))	176
Cochrane library	"Spray" OR "Spray-dried porcine plasma" AND "gut bacteria" OR "microflora" OR "microbiota" OR "microbiome"	21

2.2. Data Extraction

Two authors, FR and TK, independently analysed the abstracts and titles. In the event of disagreement, writers may reiterate the text or seek the opinion of a third author.

2.3. Quality Assessment

Two authors (FR and TK) conducted separate evaluations of the methodological quality, with a specific emphasis on identifying bias. We evaluated the potential bias in randomized controlled trials (RCTs) by employing the quality assessment approach developed by the Cochrane Collaboration [38]. We resolved disagreements by carefully checking the reference article or consulting a third author (KD).

2.4. Data Analysis

We analysed the data using RevMan 5.3 and employed the standardized mean difference to measure effect size. We used the methodologies of Wan et al. [39] to compute the mean and standard deviation of the median and range values. The term "total variability" (I^2) refers to heterogeneity. The χ^2 test was employed to assess the hypothesis of substantial heterogeneity. I^2 scores lower than 40% suggest a moderate level of heterogeneity. If there was a significant degree of heterogeneity (I^2 > 75%), the underlying cause was identified before the meta-analysis. Subgroup analysis involved the utilization of multiple comparators. We evaluated publication bias using funnel plots. p-values below 0.05 imply statistical significance.

3. Results

Out of the 541 publications initially searched, only 13 fit the specified criteria. This meta-analysis incorporated seven trials, including a total of 210 animals (**Figure 1**). The details of selected studies are given in **Table 2**.

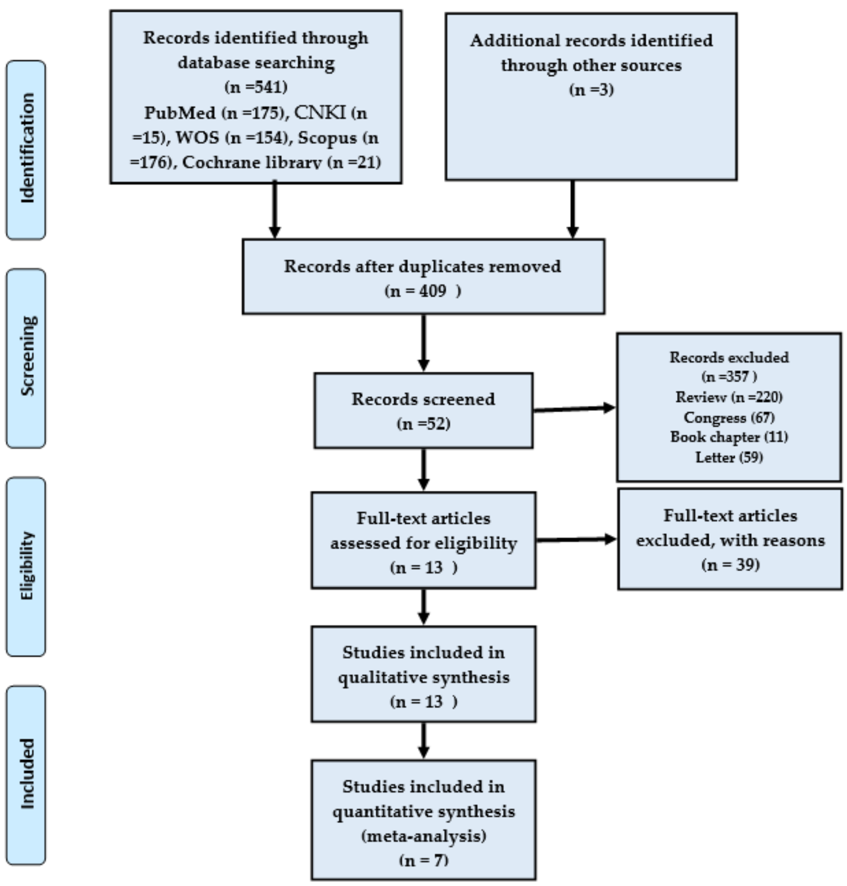

Figure 1. Prisma flow diagram of selected studies.

Table 2. Basic characteristics of the included studies.

Study ID, Reference	Number of Cases	Target Group	Study Groups	Spray %	Treatment Duration	Variables	Bacterial Change
Zhang et al., 2023 [40]	24	Landrace/Yorkshire crossbred piglets	G1: CTL G2: SDPP	6%	18 days	IL-6 and IL-10↓	Higher *Marinifilaceae*, *Fusobacterium* and *Enterococcus*
Daneshmand et al., 2023 [41]	30	Male broiler parental line chicks (Ross 308)	G1: CTL G2: SDPP	2%	28 days	IL-6, IgA, IgG and IL-10↓ IgM↑	-
Rosell-Cardona et al., 2022 [42]	27	Male SAMP8 mice	G1: CTL G2: SDPP	8%	120 days	Tlr2, Tlr4 and Tlr9, genes Muc2 and Tff3↑ Il-10 and Tgf-β↑	Increase Lactobacillus and Pediococcus, while reducing the abundance of inflammation-associated bacteria, such as Johnsonella and Erysipelothrix
Lee et al., 2022 [43]	12	healthy adult intact English pointer dogs	G1: CTL G2: SDPP	8%	28 days	TNF-α↑	Spray increased Firmicutes, which increased lactobacilli, regulatory T-lymphocyte homeostasis species, mucosal barrier restoration, and species inversely linked with pro-inflammatory cytokines.
Zh et al., 2021 [44]	192	Healthy weaning piglets	G1: NCTL G2: PCOL G3: SDPP G4: SDCP	5%	14 days	-	Decreased Bacteroidetes, increased Firmicutes, *Lactobacillus, and Streptococcus*
Crenshaw et al., 2021 [45]	452	Naïma Choice Genetics pigs	G1: CTL G2: SDPP	5%	14 days	IFN-α, IL1β, IL-4, IL-6↓ IL-10, IL-8, TNF-α, IL-12↑	-
Che et al., 2020 [46]	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 Lactobacillus and lower genera Escherichia-Shigella
Moretó et al., 2020 [47]	18	Weaned 21-day-old C57BL/6 mice	G1: CTL G2: COL G3: SDPP	8%	14 days	Tlr2, Tlr4 and Tlr9, genes Muc2 and Tff3↑ Il-10 and Tgf-β↑	Spray increased Firmicutes, which increased lactobacilli, regulatory T-lymphocyte homeostasis species, mucosal barrier restoration, and species inversely linked with pro-inflammatory cytokines.
Silva Júnior et al., 2020 [48]	108	crossbred piglets	G1: NCTL G2: PCOL G3: SDPP G4: SDCP	-	65 days	-	Lower concentration of Escherichia-Shigella and Campylobacter
Tran et al., 2018 [49]	96	weaned pigs	G1: CTL G2: SDPP	5%	28 days	-	*Clostridiaceae* increased on day 14, but decreased on day 28 Decreased *Veillonellaceae* on day 14 and *Lachnospiraceae* overally
Zhang et al., 2015 [50]	144	normal birth weight weaned pigs	G1: NCTL G2: PCOL G3: SDPP G4: SDCP	5%	28 days	-	Decreased the populations of E. coli The population of Lactobacillus increased
Gisbert et al., 2015 [51]	40	Gilthead sea bream fry	G1: CTL G2: SDPP	6%	14 days	Nonspecific immune responses↑	-
van Dijk, 2002 [52]	68	normal birth weight piglets	G1: CTL G2: SDPP	5%	14 days	-	influencing the gastrointestinal microflora

Note: G, group; CTL, control diet; COL, low doses of neomycin and colistin; SDPP, spray-dried porcine plasma; NCTL, negative basal diet; PCTL, positive control; SDCP, spray-dried chicken plasma protein.

The SDP group showed statistically lower IL-10 (SMD: −1.79, 95%CI: −2.43, −1.15, I^2: 60%, p = 0.04) than the control group (**Table 3, Figure 2**). While IL-1β (SMD: 2.83, 95% CI: 0.48, 5.18, I^2: 91%, p = 0.02) and IL-6 (SMD: 3.09, 95% CI: 1.47, 4.72, I^2: 86%, p = 0.0002) were significantly higher in SDP-fed animals than the control group (**Table 3, Figure 2**). The SDP group showed statistically higher TNF-α (SMD: 2.32, 95% CI: 0.74, 3.89, I^2: 92%, p = 0.004) than the control group (**Table 3, Figure 2**). Also, the SDP group showed statistically higher IgG (SMD: 0.59, 95% CI: 0.03, 1.15, I^2: 54%, p = 0.04) than the control group (**Table 3, Figure 2**). Additional cytokines were either mentioned in a limited number of studies that were not included in the analyses for statistical reasons, or they exhibited insignificant alterations in the animals fed with SDP compared to the control group (**Table 3, Figure 2**).

Table 3. The alteration of cytokine serum levels in response to SDP diet.

Immunologic Factors	No. of Trials	No. of Participants	SMD	95% CI	*p*	I^2 (%)	*p* for Heterogeneity
IFN-α, pg/mL	1	24	-	-	-	-	-
IFN-γ, pg/mL	1	25	-	-	-	-	-
IL-10, pg/mL	5	184	−1.79	−2.43, −1.15	0.04	60%	<0.00001
IL-1β, pg/mL	3	70	2.83	0.48, 5.18	0.02	91%	<0.00001
IL-4, pg/mL	1	25	-	-	-	-	-
IL-6, pg/mL	4	100	3.09	1.47, 4.72	0.0002	86%	<0.00001
IL-8, pg/mL	1	25	-	-	-	-	-
TNF-α, pg/mL	4	166	2.32	0.74, 3.89	0.004	92%	<0.00001
IL-12, pg/mL	1	25	-	-	-	-	-
MDA, μM	3	81	−0.38	−0.96, 0.20	0.2	37%	0.2
SOD, U/mL	2	42	−0.65	−2.79, 1.49	0.55	89%	0.003
TAS, mmole/L	1	24	-	-	-	-	-
GPx, U/L	3	84	−0.79	−3.18, 1.60	0.52	94%	<0.00001
IgA, mg/mL	1	30	-	-	-	-	-
IgM, mg/mL	2	126	0.23	−0.12, 0.58	0.19	0%	0.90
IgG, mg/mL	3	150	0.59	0.03, 1.15	0.04	54%	0.11

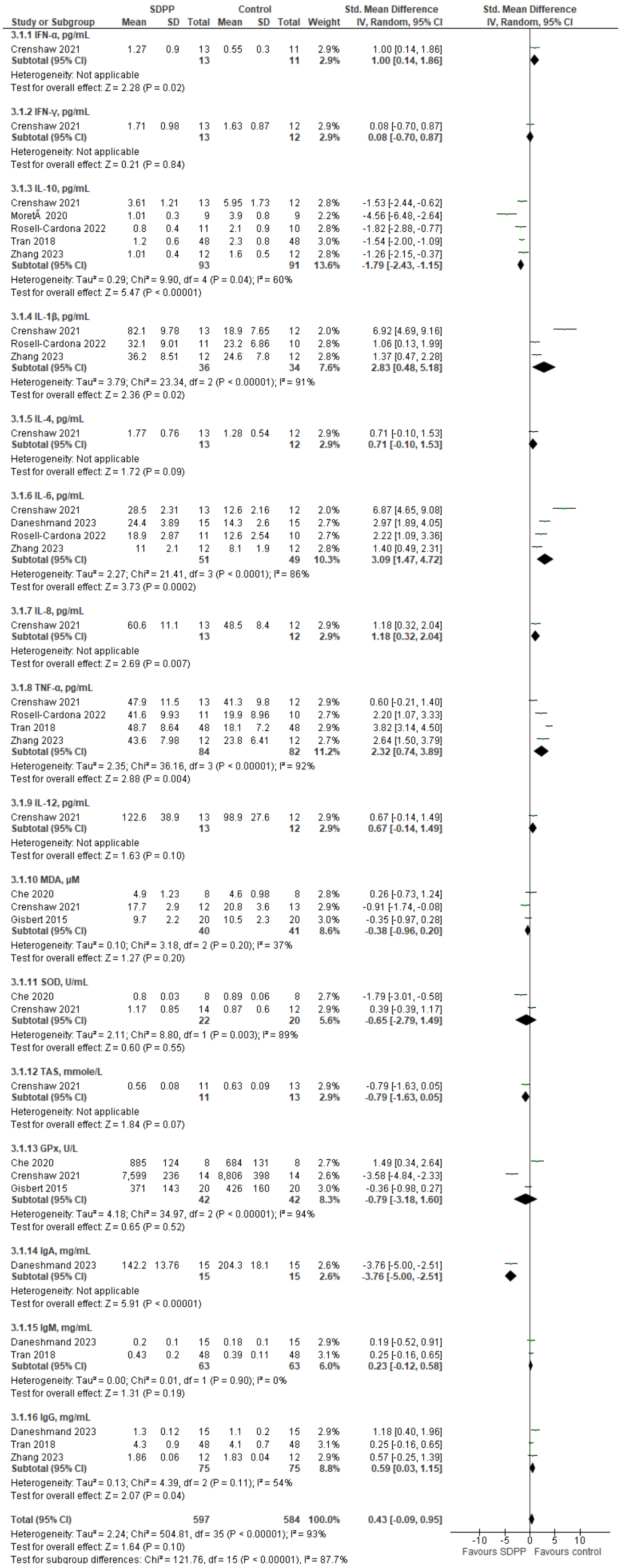

Figure 2. Forest plot of the alteration of cytokine serum levels in response to SDP diet.

Figure 3 comprehensively analyses the potential bias associated with each study. Insufficient information on blinding prevented all investigations from assessing the risk of bias, which was shown to be significant. All 13 trials exhibited suitable randomization and allocation concealment, resulting in a minimal risk of bias (**Figure 3**).

Figure 3. Risk of bias among selected studies.

The empirical research methodologies developed by Begg and Egger were used to evaluate the presence of publication bias. In addition, it was necessary to visually assess the symmetry of funnel plots (**Figure 4**).

The statistical tests revealed a negligible probability of editorial bias ($p > 0.05$). The robustness and consistency of the results were assessed by subjecting the eleven publications included in the meta-analysis to a sensitivity analysis. The overall impact magnitude remained stable even after excluding individual study articles, reinforcing the credibility of the conclusions obtained from this meta-analysis.

4. Discussion

As far as we know, no comprehensive analysis has assessed the alteration of immunologic components and cytokines in response to diets that include plasma products. This article presents the findings of a meta-analysis that investigates the effects of a diet including SDP on changes in immunologic variables and cytokines. We aim to tackle the reproducibility problem in microbiome-diet research and provide recommendations for further experimental inquiry in targeted areas. Although our examination was limited to only 13 research studies, it is essential to highlight that this specific set of studies covers a wide range of technologies used, sequencing targets, and rodent models explored.

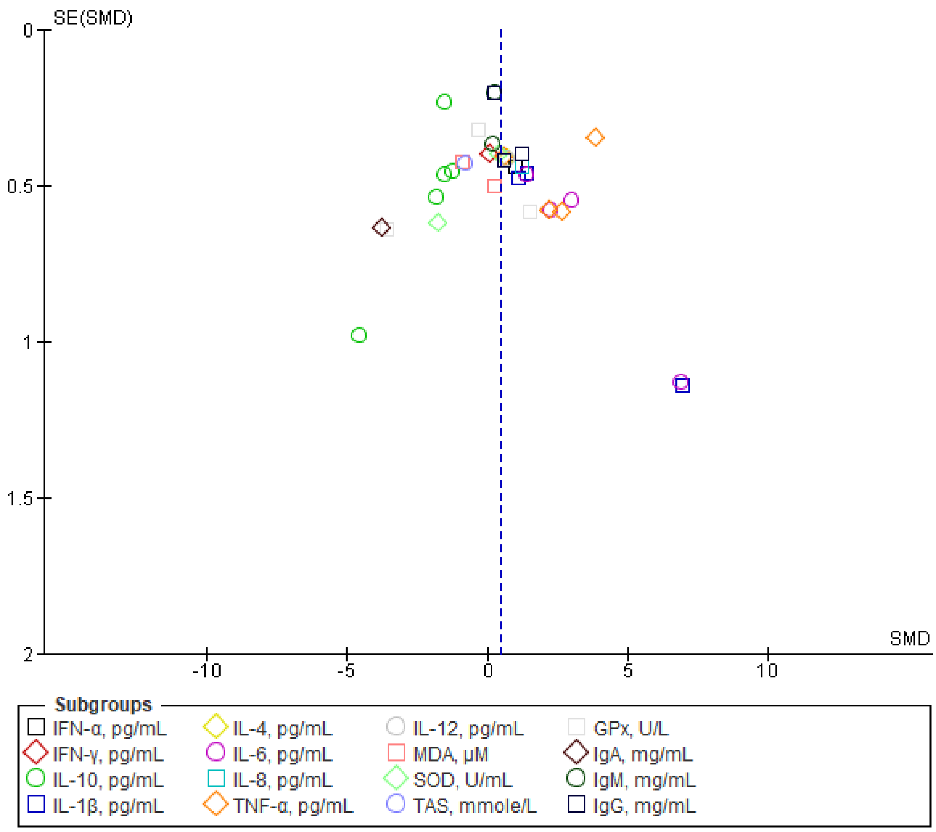

Figure 4. Funnel plots of the alteration of cytokine serum levels in response to SDP diet.

Supplementing the diet with SDP can regulate the immunological response of gut-associated lymphoid tissue. Increasing SDP decreases both acute mucosal inflammation and chronic inflammation linked to aging. The present meta-analysis revealed a significant decrease in IL-10 following the use of the SDP diet. In contrast to our findings, Miró et al. [53] investigated whether supplementing with SDP may improve colitis symptoms in a genetic mouse model of inflammatory bowel disease (IBD) by feeding either a control diet or a diet supplemented with SDP to wild-type and Mdr1a knockout mice. They demonstrated that SDP reduced the production of inflammatory cytokines and raised the levels of the anti-inflammatory IL-10 in the mucosa lining the colon. Garcia-Just et al. [54] examined whether the anti-inflammatory effects of SDP may improve age-related cognitive decline and maintain brain homeostasis in a senescence mouse model. An elevation in the IL-10 concentration, a cytokine known for its anti-inflammatory properties and its association with memory retention, was noted during the observation. In accordance with our research, Maijó et al. [13] investigated the impact of oral SDP supplementation on the lung adaptive immune response in mice exposed to intranasal LPS. The researchers showed that SDP administration resulted in an elevation of IL-10 production in the intestinal mucosa of non-inflamed mice, leading to a decrease in the activation of the basal immune system. The discrepancy may be attributed to the disparity in IL-10 levels between the bloodstream and the mucosal tissue and the choice of animal model [55].

The present study demonstrated that IL-1β and IL-6 were significantly higher in SDP-fed animals than in the control group. Fernández-Alacid et al. [56] examine the mucosal immune response by testing the antibacterial potential of skin mucus and the systemic immune response by studying splenocytes *ex vivo* with a pathogen-associated molecular pattern. The study demonstrated a substantial increase in IL-1β levels at 24 hours in splenocytes of fish fed the SDP diet compared to the control group.

In the present meta-analysis, the SDP group showed statistically higher TNF-α and IgG than the control group.

According to Peace et al. [57], pigs with a diet containing 5% SDP for 14 days after being weaned experienced decreased intestinal inflammation. This was evidenced by lower levels of TNFα in the intestinal tissue and a lower fecal score. Additionally, the pigs showed improved intestinal barrier function, as indicated by increased trans-epithelial electrical resistance and decreased short-circuit current. Furthermore, there was a reduction in the movement of mannitol and inulin from the mucosal to the serosal side of the intestine. Therefore, SDP may affect intestinal inflammation by enhancing the barrier's integrity and regulating the immune response in the mucosal lining.

This analysis aimed to identify the consistent characteristics of the gut microbiota's response to the SDPP diet despite the variations and challenges encountered in replicating basic ecological measurements in different studies. This identification will help pinpoint specific areas for further mechanistic research. The results were acquired through data analysis from multiple laboratories. They offer a solid foundation for future research focused on comprehending the correlations between alterations in microbial ecology, dietary intake, and their impact on host well-being and illness.

5. Implications

Animal models have long played a crucial role in medical research, not only due to the broad biological commonalities shared among mammals but also because many human diseases manifest similarly in other species. This has allowed scientists to study disease mechanisms and develop medical treatments that have significantly advanced healthcare. However, despite the genetic similarities between humans and the animal models used in research, distinct genetic differences exist, influencing how diseases and treatments manifest across species. While some argue that these differences undermine the validity of animal-based research, many researchers advocate for a deeper understanding of these variations and their integration into experimental design and data interpretation.

Animal models have been instrumental in drug development and the study of biochemical processes within the body. However, interspecies differences in physiology can sometimes lead to unexpected results when translating findings from animals to humans. For example, serotonin-derived drugs successfully tested in animal models, such as dogs, later led to severe adverse effects in humans, including chest pain, heart attacks, and fatalities. This highlights the importance of selecting the appropriate animal models and carefully considering species-specific responses when developing therapeutic interventions.

Spontaneous animal models, in which diseases naturally occur in the studied species, have been particularly valuable. For instance, dogs are the only spontaneous animal model for prostate cancer, making them crucial for studying this significant human health issue. Similarly, animal models play a pivotal role in tissue engineering, where *in vivo* testing remains essential for developing and validating new approaches before regulatory approval. Despite advancements in 3D printing and bioreactor technologies, *in vivo* studies help ensure efficacy and safety, although challenges such as scaling and structural penetration must still be addressed.

In addition to their role in disease research and drug testing, animal models have provided key insights into nutrition and immune function. A recent study investigating the immune response to SDP in animal models has revealed several important public health implications, particularly in nutrition, immune modulation, and disease prevention. The findings suggest that dietary interventions, such as the inclusion of SDP, can influence immune responses by modifying cytokine profiles and promoting anti-inflammatory effects. This has potential applications in managing inflammatory conditions in humans, such as inflammatory bowel disease and allergies, through the development of functional foods or dietary supplements aimed at enhancing gut health and overall immunity.

The study further emphasizes the critical relationship between diet and gut microbiota, which, in turn, affects immune homeostasis. A balanced diet rich in prebiotics, probiotics, and functional foods is increasingly recognized as essential for preventing gastrointestinal and immune-related diseases. Public health initiatives could focus on educating populations about dietary strategies that support gut health, thereby reducing the burden of chronic diseases.

Beyond human health, the study's findings suggest that SDP may reduce the need for antibiotics in livestock farming by enhancing immune responses and decreasing inflammation. This has significant implications for antimicrobial resistance (AMR), a pressing global concern. Encouraging the use of immune-boosting feed additives like SDP could mitigate antibiotic overuse in agriculture, ultimately benefiting both animal and human health.

The study also highlights the potential of SDP in managing chronic inflammatory diseases by reducing proinflammatory cytokines and increasing anti-inflammatory markers. This could lead to alternative therapeutic approaches for conditions such as arthritis, asthma, and autoimmune disorders, potentially reducing the dependence on immunosuppressive drugs that often come with severe side effects. Moreover, SDP's ability to enhance immune markers like IgG may be particularly beneficial for immunocompromised individuals, including those undergoing chemotherapy, HIV patients, and the elderly, supporting their immune function and reducing the risk of infections.

Ensuring food security and safety is another crucial aspect of public health that ties into the study's findings. Access to nutrient-rich foods is fundamental in preventing malnutrition and associated immune deficiencies, particularly in low-resource settings where infectious diseases are prevalent. Policies prioritizing food safety and nutrition could help strengthen immune resilience across populations.

Additionally, improving immune health in livestock through dietary interventions could reduce the risk of zoonotic diseases, which are transmitted from animals to humans. Healthier animals are less likely to harbor and spread infectious pathogens, making nutrition-based approaches a valuable preventive strategy against emerging global health threats.

Finally, the economic and environmental benefits of such dietary interventions should not be overlooked. Healthier livestock could lead to reduced veterinary costs and increased agricultural productivity, providing economic advantages for farmers and contributing to sustainable food production. Public health policies promoting sustainable agricultural practices, including the use of immune-enhancing feed additives, could help balance economic growth with environmental conservation.

The integration of animal models in biomedical research has significantly advanced medical knowledge, drug development, and therapeutic strategies, despite the challenges posed by species differences. The findings on SDP's immune-modulating effects further emphasize the critical role of dietary interventions in public health, offering potential strategies for improving immune health, preventing disease, and reducing antibiotic dependency in agriculture. Future research and public health initiatives should continue exploring such approaches to enhance overall well-being in both human and animal populations. Drugs that are derived from animal blood or other products may be associated with allergic and immune responses. Mostly such drugs are administered through the injection route, but sometimes to reduce side-effects, they are given by inhalation of a nasal spray. A drug allergy is an inappropriate reaction of the immune system to a medication. Any medication, even over-the-counter or herbal remedies, can cause drug allergy symptoms! However, some medications are more likely to cause allergies. The most common signs and symptoms of a drug allergy are hives, itching, and fever. However, a drug allergy can be even more dangerous, causing damage to multiple body systems and a condition called anaphylactic shock, which is dangerous and potentially fatal! Note that drug allergy is different from drug side effects (known and possible reactions that are listed on the medication guide) and drug toxicity (toxicity caused by taking too much of a medication).

6. Strengths and Limitations

This review was performed on studies that used animal models. An animal model is a living, often genetically engineered, laboratory animal that is used in the process of researching and studying human diseases *in vivo* in order to better understand the mechanism of the disease, without the risk of harming humans. In animal model induction research, various types of laboratory mice and rats, as well as other types of laboratory animals such as rabbits and hamsters, are typically used. By using various methods, including genetic, physical, and chemical, various disease models are created and induced in laboratory animals. After the created model is confirmed, research and study objectives are carried out on the induced disease model. Throughout history, ethical considerations and social prohibitions have prevented experimental studies of biology and pathobiology on human samples. As a result, most of our current basic knowledge of human biology, physiology, hormonology, and pharmacology has been obtained from initial studies of mechanisms in animal models. The creation of animal models is not only due to ethical principles, but often, easy access, economic, and scientific reasons make initial studies in animals the most suitable solution for studies of a biological mechanism. The use of animal anatomy and physiology models has contributed significantly to the advancement of science and research in the field of health. In this way, various animal models have been created in order to study the process of treatment progress and molecular and genetic studies of various diseases. These animal models have been categorized as cancer, clinical, surgical, drug studies, toxicology studies, medical research, regenerative medicine, and tissue engineering models. Tissue and gene research laboratories have so far succeeded in creating the following laboratory models in rats and mice, which can be fully guaranteed to provide these types of models to dear researchers in the shortest possible time and at a reasonable price. Combining data has several advantages. First, it increases the power of the test (reducing the probability of type II error). Second, it increases the accuracy of the effect estimate. Third, it answers questions that primary studies cannot answer because some variables are considered constant in primary studies (such as gender and age group). Therefore, each of the primary studies cannot answer the effect of variables that were constant alone, but meta-analysis has solved this problem. Fourth, it allows for a more accurate assessment of differences between study findings, since it is quite natural for different and even contradictory results to exist in different studies. However, one of the disadvantages of combining data is the problem of data heterogeneity or inconsistency. If the tests in question are fundamentally different, combining them is illogical and should be avoided.

7. Conclusion

To summarize, our results indicate that adding SDP to the diet decreases the number of activated cytokine-related cells in mice. Additionally, SDP alters the secretion of cytokines, which promotes an immune profile that is anti-inflammatory. Ultimately, this series of events leads to a decrease in the production of molecules that promote inflammation in the lining of the colon and a restoration of the protective characteristics of the cells that make up the colon's lining. The positive impact of SDP in this model indicates that these supplements may play a role in enhancing and modulating the immune response. The historical trend indicates an increasing sensitivity to the use of animals in the biological and medical sciences, ranging from a complete disregard for animal rights in the recent past to the adoption and enforcement of binding regulations and the formation of legal institutions in the present. Recent scientific evidence indicates the ability of animals to experience a variety of pain and emotions, suppressing symptoms of acute and chronic pain in the presence of humans. It has also been shown that some animals, due to the lack of compensatory mechanisms for pain, can experience more intense distress and fear than humans. The existence of basic emotional systems such as anger, panic, fear, depression, and post-traumatic stress has been described in animals, and many animals have shown verbal skills, problem-solving skills, instrumental cognition, suggestion, and self-awareness, and evidence of causal reasoning, flexible learning strategies, imagery, foresight, and play. These characteristics and abilities support the issue of quality of life in animals and can provide a basis for ethical support and protection, as well as guidelines for the exploitation of animals.

Author Contributions

All authors contributed equally to the conception, design, data collection, analysis, and writing of this study. All authors have read and agreed to the published version of the manuscript.

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All data presented in the manuscript.

Conflicts of Interest

The authors declared no conflict of interest.

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