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Review

Bacterial Community Diversity, Richness, and Possible Immunotherapies Association in Response to Spray-Dried Porcine Plasma-Fed Diet: An Animal Model

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Abstract: This study aims to demonstrate the significance of employing non-invasive dietary intervention to control the diversity and abundance of bacterial communities in feces. The indexing databases Scopus, PubMed/Medline, ISI Web of Science, Embase, Cochrane Central, and CINAHL were extensively searched. Only 13 of 541 papers found in the initial searches met the criteria. Seven studies involving 210 animals were included in this meta-analysis. The SDPP group showed statistically lower Shannon (SMD: 1.20, 95% CI: 0.22–2.19, I^2: 88%, $p = 0.02$) and Chao1 (SMD: 2.95, 95% CI: 1.99–3.91, I^2: 77%, $p < 0.00001$) indices than the control group. The SDPP-diet fed group showed notably lower OTU counts compared to the control group (SMD: 2.99, 95% CI: 0.67–5.32, I^2: 97%, $p = 0.01$). The *Firmicutes/Bacteroidetes* ratio is reliably increased following the SDPP-fed diet (SMD: 0.68, 95% CI: 0.13–1.23, I^2: 0%, $p = 0.02$). While noticeable differences existed between studies and difficulties were encountered in replicating basic ecological measurements, the purpose of this analysis was to identify the consistent characteristics of the gut microbiota's response to the SDPP diet, thereby pinpointing specific areas for further mechanistic research.

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

1. Introduction

The colon hosts a rich ecosystem of gut bacteria. Alterations in gut microbiota—whether in composition or function—significantly influence immune response, metabolism, and neurobehavioral characteristics, hence affecting health and disease [1]. The composition of gut microbiota might vary significantly among individuals. Nevertheless, numerous critical bacterial species are frequently identified in most instances. Diet is thought to influence microbial structural variances in mice, accounting for over 50% of these differences. Diet is anticipated to account for 20% of these variations in people, suggesting the potential for dietary treatments in disease management through the modulation of gut microbiota [2,3]. Studies have shown that human microbiota can swiftly adapt to short-term, drastic dietary alterations. However, these alterations persist for several days [4]. Alpha diversity refers to the

average species variety within many localized ecosystems or locations [5]. Robert Harding Whittaker coined this expression, along with the associated notions of beta diversity (β-diversity) and gamma diversity (γ-diversity) [6]. Analyzing community surveys often involves summarizing and comparing alpha diversity, a prevalent method due to the factors that may influence it.

The primary method for assessing differences in microbial habitats in microbial ecology studies is the analysis of alpha diversity from amplicon sequencing data. Species abundance refers to the number of species or operational taxonomic units (OTUs) within a particular geographical area. Regarding alpha diversity measurements, it is the most straightforward. Nonetheless, numerous supplementary metrics or indices exist that account for the frequency or abundance of OTUs. The manifestation of dispersion is commonly noted while utilizing an octave plot. Different ecologists have variously characterized alpha diversity. Varied assumptions concerning species diversity can affect the various categories. Consequently, numerous investigations have employed various diversity indices [7].

According to a recent study conducted by researchers at the Center for Cancer Research at the National Cancer Institute (NCI) [8], a high-fiber diet could potentially enhance the response to immunotherapy in some melanoma patients by affecting their gut microbiome. The study found that among patients with advanced melanoma receiving immune checkpoint blockers, those who consumed more fiber daily lived the longest without disease progression. On the other hand, the use of probiotic supplements seemed to slightly diminish the effectiveness of this form of immunotherapy. Probiotics are live microorganisms that are commonly taken as supplements to improve gut health. Consequently, researchers suggest that targeting the composition of the gut microbiota can affect a patient's capacity to react to immunotherapy. Immunotherapy using immunomodulatory drugs aids in reactivating the immune system's inherent ability to identify and destroy tumor cells. These medications have proven highly effective in treating melanoma, extending the lives of some individuals with advanced stages of the disease by years [9]. Although for the majority of patients, this treatment does not prevent tumor growth. Research has indicated that the makeup of gut bacteria may play a role in how patients respond to immunotherapy.

Animal nutritionists have demonstrated that spray-dried porcine plasma (SDPP), a by-product of pig slaughter, benefits both cattle and commercial aquatic species [10]. SDPP is a potential immunomodulatory agent for immunotherapy, rich in bioactive proteins, immunoglobulins (IgG), and anti-inflammatory compounds. The elevated IgG levels in SDPP facilitate passive immunotherapy by eradicating germs and enhancing the immune response. Trials conducted on pigs demonstrated a reduction in diarrhea infections [11]. Furthermore, SDPP modulates the body's inflammatory responses by decreasing pro-inflammatory cytokines (such as TNF-α and IL-6) and increasing anti-inflammatory mediators (such as IL-10). This mechanism resembles that of immunotherapy in treating autoimmune and chronic inflammatory diseases [12]. The incorporation of SDPP into poultry vaccines enhanced their efficacy, indicating that it possesses adjuvant-like properties that may complement active immunization. Capacity of SDPP. Its capacity to enhance gut barrier integrity, crucial for mucosal immunity, renders it a potential adjunct to oral immunotherapy (OIT) for food allergies or inflammatory bowel disease [13]. Traditional immunotherapies, such as monoclonal antibodies, are effective solely on specific routes. SDPP is a comprehensive, economical alternative for enhancing the immune system. Further research is required to validate its therapeutic efficacy in combination with immunotherapy regimens. Dietary SDPP increased intestinal goblet cell density without significantly altering the autochthonous microbiota, as reported in previous research. However, there is a lack of information regarding the potential processes that occur in the gut of gilthead sea bream when given a diet containing SDPP. This study aims to demonstrate the significance of employing non-invasive dietary intervention to control the diversity and abundance of bacterial communities in feces.

2. Methods

This meta-analysis adhered meticulously to the (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline and MOOSE (Meta-analyses of Observational Studies in Epidemiology) standards [14,15].

2.1. Search Strategy

The indexing databases Scopus, PubMed/Medline, ISI Web of Science, Embase, Cochrane Central, and CINAHL were extensively searched. The search was conducted 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])) from January 1, 1980, to December 16, 2023, without Clinicaltrials.gov and the WHO clinical trials search site were also evaluated. We also manually searched archives cited in the articles.

2.2. Study Selections

Animal models investigating the effects of SDPP on intestinal function, oxidative status, intestinal microbiota composition, and immunologic biomarkers were included. Shannon, Chao1, and Simpson alpha diversity indices were used to compare bacterial community diversity among the treatments [16]. Additionally, the richness of the bacterial community and the *Firmicutes/Bacteroidetes (*F/B*)* ratio were measured. Moreover, two authors (FR and TK) examined the abstracts and titles separately. If they disagree, authors would quote the text again or consult a third author.

2.3. Evaluation of Quality and Potential Bias Risks

Two authors (FR and TK) independently assessed methodological quality, focusing on bias. We assessed RCT bias using the Cochrane Collaboration's quality assessment method [17]. We resolved disagreements by carefully checking the reference article or consulting a third author (KD). We examined the data in RevMan 5.3 and utilised the standardised mean difference as the effect size. We applied the methods of Wan et al. [18] to calculate the average and variability of the median and range data.

2.4. Data Analysis

Heterogeneity was referred to as "total variability" (I^2). The $\chi 2$ test was used to evaluate the hypothesis of significant heterogeneity. I^2 scores below 40% indicated modest heterogeneity. If heterogeneity was significant (I^2 > 75%), the cause was identified before meta-analysis. Multiple comparators were used for subgroup analysis. We assessed publication bias with funnel plots. *p*-values under 0.05 indicated significance.

3. Results

Only 13 of 541 papers found in the initial searches met the criteria. Seven studies involving 210 animals were included in this meta-analysis. The SDPP group showed statistically lower Shannon (SMD: 1.20, 95% CI: 0.22–2.19, I^2: 88%, $p = 0.02$) and Chao1 (SMD: 2.95, 95% CI: 1.99–3.91, I^2: 77%, $p < 0.00001$) indexes than the control group (**Figure 1**). SDPP-fed animals had similar Simpson and ACE index values to those of the controls (**Figure 1**). The SDPP-diet fed group showed notably lower OTU counts compared to the control group (SMD: 2.99, 95% CI: 0.67–5.32, I^2: 97%, $p = 0.01$) (**Figure 1**). The *Firmicutes/Bacteroidetes* ratio is reliably increased following the SDPP-fed diet (SMD: 0.68, 95% CI: 0.13–1.23, I^2: 0%, $p = 0.02$) (**Figure 2**). **Figure 3** presents a comprehensive overview of the bias risk associated with each particular study. Due to a lack of information regarding blinding, all investigations were unable to determine the risk of bias, which was found to be substantial. All 12 studies were found to have appropriate randomization and allocation concealment, resulting in a low risk of bias. Begg and Egger's empirical research approach was employed to evaluate the existence of publication distortion. Furthermore, it was deemed essential to conduct a visual assessment of funnel plots to determine their symmetry (**Figure 4**). The statistical tests indicated a minimal likelihood of editorial bias ($p > 0.05$). The strength and reproducibility of the findings were evaluated through a sensitivity analysis of the eleven publications included in the meta-analysis. Even when removing individual study papers, there was minimal fluctuation in the overall impact magnitude, which further supports the reliability of the findings from this meta-analysis.

4. Discussion

To our knowledge, no systematic review has evaluated the change in gut bacterial community diversity and richness in response to diets containing plasma products. In this study, we present the findings of a meta-analysis that examines the effect of a diet containing SDPP on the gut microbiome. Our goal is to address the issue of reproducibility in microbiome-diet research and recommend specific areas for future experimental investigation. Despite our limited examination of only 13 studies, it is noteworthy that this particular set of studies encompasses a diverse

array of technologies utilised, sequencing targets, and rodent models investigated.

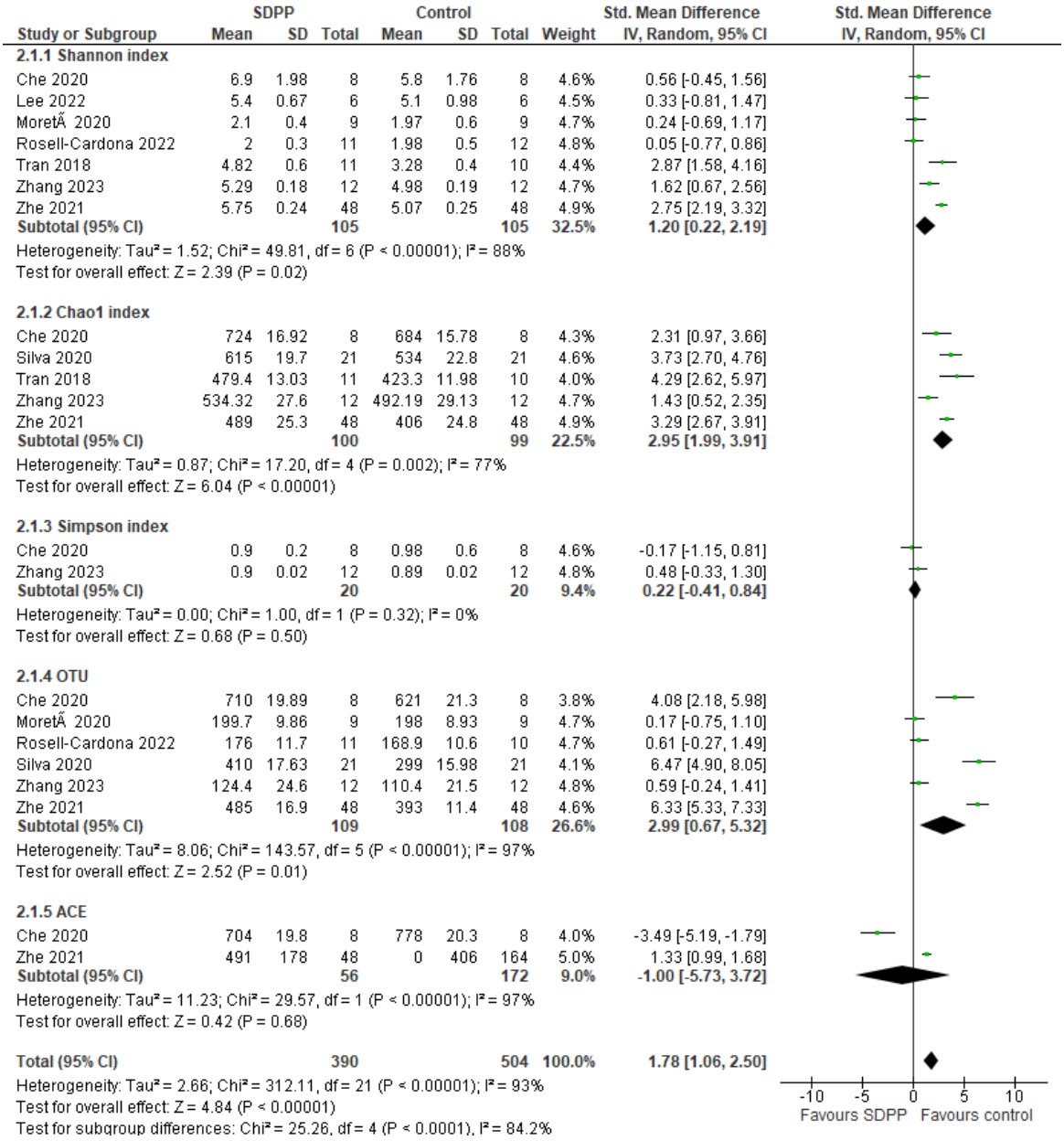

Figure 1. Forrest plot of the variety and abundance of bacterial populations in feces in response to SDPP-fed diet.

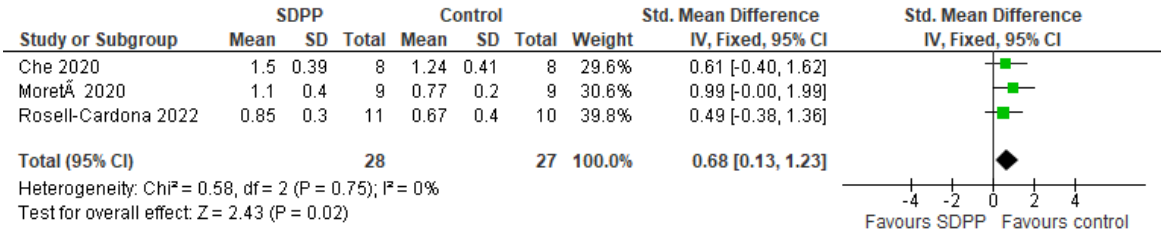

Figure 2. Forest plot of *Firmicutes/Bacteroidetes* ratio changes following SDPP-fed diet.

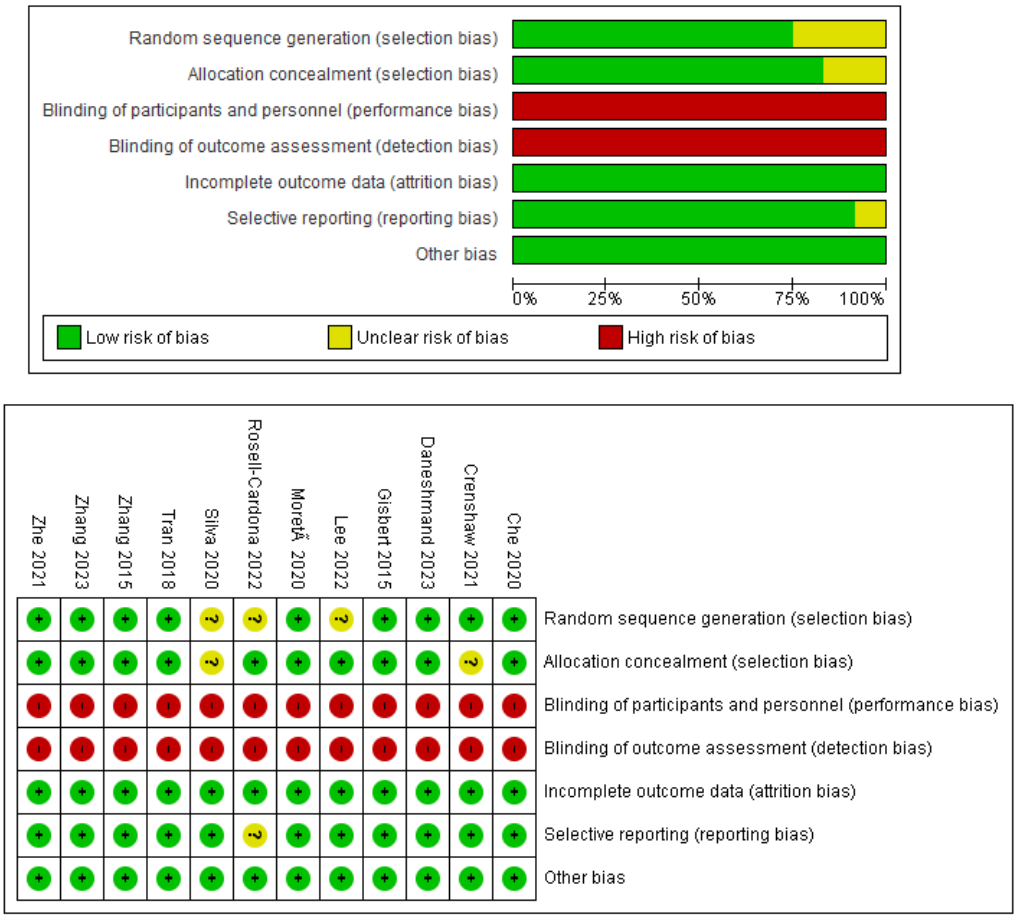

Figure 3. Risk of bias among selected studies.

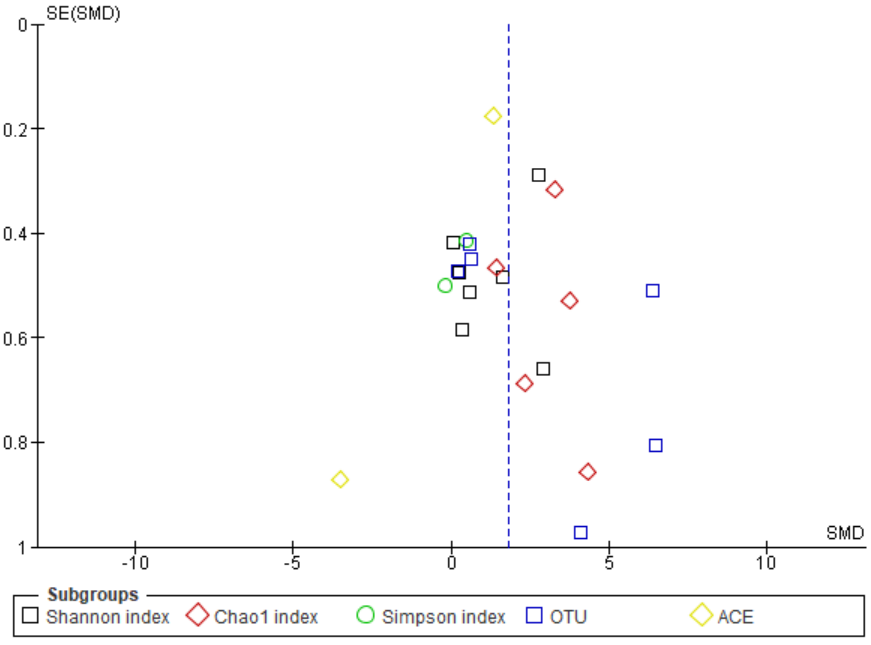

Figure 4. Funnel plots of bacterial community diversity and richness in response to SDPP.

SDPP, a prominent component in animal feed, has been found to possess excellent palatability. It effectively enhances feed consumption in weaning piglets, reducing the time required for the transition from weaning to start feeding [19]. The intestinal microbial communities have adjusted to the host's health and growth performance by adapting to the environment and nutrients in the intestinal lumen [20]. The present study reported a reduction in microbial diversity (measured by OUT, Shannon, and Chao1 indices) when piglets were fed a diet containing SDPP. This finding contradicts a recent study that demonstrated an enhancement in bacterial diversity with the presence of SDPP [21]. This disparity may be attributed to the substantial variation in the gut microbiota of typical pigs [22].

Remarkably, the F/B ratio consistently rises after consuming the SDPP diet. Initially, early research on obesity revealed a notable increase in this ratio. However, it has been found that this ratio is not a consistent indicator when studying BMI in different groups of people [23,24]. The relationship between BMI and nutritional intake is distinct, and the consequences of varying responses in the F/B ratio alteration between mice given a standard diet and obese humans remain uncertain [25]. Recent research suggests that using refined SDPP instead of more intricate diets may be the cause [26].

4.1. How Diet Can Help Immunotherapy

A recent study discovered that a Mediterranean diet may enhance immunotherapy responses in individuals with advanced melanoma, the most aggressive form of cancer [27]. The researchers found that a Mediterranean diet, rich in fiber, monounsaturated fats, and polyphenols, was associated with improved immunotherapy response rates and longer progression-free survival in patients with advanced melanoma. This diet, which contains monounsaturated and polyunsaturated fats from olive oil, nuts, and fish, as well as polyphenols and fiber from vegetables, fruits, and whole grains, was associated with significantly improved responses to immunotherapy drugs called checkpoint inhibitors [28]. Inhibitors, among the most successful treatments for melanoma to date, function by targeting immune system checkpoints, thereby stimulating the body's T cells to recognize and destroy cancer cells.

4.2. Bacteria Enrichment, Immunotoxins and Cancer Therapy

A few relevant papers from the late 1970s characterized the cell-destroying capabilities of immunotoxins, which influenced the development and future trajectory of this technology [29]. A study proposed that diphtheria toxin could kill mammalian cells, and further research revealed that a single molecule of diphtheria toxin could destroy an individual cell, demonstrating the potential of diphtheria toxin and similar substances [30]. The effectiveness of the toxin depends on the duration and stability of its enzymatic domain inside the cell. In another study, scientists used antibodies to direct the toxins' lethal effects toward specific targets. Specifically, they explored the use of anti-lymphocyte antibodies to target and eliminate lymphoblastic tumor cells. By chemically linking diphtheria toxin to these antibodies, they turned the antibodies into primary immunotoxins [31]. Later, monoclonal antibodies were modified, and immunotoxins containing monoclonal antibodies that targeted specific antigenic epitopes were developed [32]. For some time, the chosen monoclonal antibodies were chemically linked to the desired toxins, resulting in the creation of new immunotoxins, primarily for cancer treatment.

The following leap involved the application of molecular cloning techniques, enabling the creation of fusion proteins (immunotoxins) made by linking antibody fragments to enzymatically active toxin domains. Immunotoxins for cancer treatment have followed a predictable path of development and progress over the past 30 years [33]. Clinical trials were then designed and conducted on animal tumor models. Different immunotoxins derived from plant toxins, such as ricin, or bacterial toxins, like diphtheria toxin and exotoxins, have been tested to date only in *Pseudomonas*, which have entered clinical trials [34]. A targeted toxin called IL-2-DT against the IL-2 receptor has been approved for use in humans [35]. While immunotoxins show great promise, they have also been combined with other agents for treatment. Additionally, immunotoxins have applications in areas such as immune response regulation, including the removal of T cells from connective tissue or the elimination of regulatory T cells, as well as antiviral activity [36].

SDPP alters immune cell functionality by elevating the Firmicutes/Bacteroidetes (F/B) ratio, thereby promoting gut health and modulating the overall immune system. The bioactive components of SDPP, including immunoglobulins and growth factors, enhance the integrity of the gut barrier, increase beneficial Firmicutes (such as Lactobacillus), and reduce pro-inflammatory Bacteroidetes [37]. The elevated F/B ratio enhances the population of bacteria that produce short-chain fatty acids (SCFAs). These short-chain fatty acids (SCFAs) subsequently activate regula-

tory T cells (Tregs), which combat inflammation and inhibit Th17 responses by blocking histone deacetylase [38]. Furthermore, increasing the F/B ratio by SDPP reduces LPS from Bacteroidetes, thereby diminishing TLR4/NF-κB activation and the synthesis of pro-inflammatory cytokines [39]. The immunomodulatory advantages encompass enhanced secretion of mucosal IgA and reduced systemic inflammation, positioning SDPP as a potential dietary intervention for immune-related disorders.

Bacterial vaccines and immunotherapies are often designed to modulate the immune system in specific ways, such as through the use of checkpoint inhibitors. SDPP is a nutritional alternative that influences several immunological systems. The elevated immunoglobulin concentration may function akin to passive vaccination to eliminate pathogens, and its impact on gut microbiota (such as the F/B ratio) resembles the adjuvant-like effects shown in other oral vaccines. Future research may investigate the incorporation of SDPP as an adjunct to vaccination protocols.

Cancer is recognized as one of the leading causes of death globally, with the number of cases rising each year [40]. Current treatments are not only inadequate but also lead to numerous side effects. Biotechnology, utilizing recombinant DNA methods, has played a crucial role in the production of drugs and vaccines [41]. Recombinant products, which are produced by manipulating various organisms with genetically engineered DNA and modifications, have led to a significant transformation in pharmaceutical products, resulting in the widespread use of high-molecular-weight pharmaceuticals, including recombinant proteins, instead of small chemical molecules. Today, protein therapy methods are widely used to treat cancer [42]. Except for a handful of pharmaceutical proteins isolated from natural sources, most therapeutic proteins currently used are recombinant proteins or monoclonal antibodies. Additionally, about 133 recombinant drugs for the management of different illnesses, especially cancer, AIDS, and nervous system disorders, are in various stages of clinical trials [43].

Researchers, who first reported the differential staining of various tissues in 1971, argued that it was possible to develop agents specifically to kill cancer cells [44]. The discovery of monoclonal antibodies and the ability to produce large quantities of these antibodies that react with specific antigens on cancer cells created a desire to use toxins to kill cancer cells. By attaching these toxins to monoclonal antibodies, new agents were designed to target and kill tumor cells; these agents are called immunotoxins [45]. Today, a wide variety of organisms and expression systems are available for producing recombinant proteins. However, *Escherichia coli* (*E. coli*) is one of the most common hosts used for recombinant protein production due to its rapid proliferation, availability of suitable systems for genetic manipulation, knowledge of its genetic structure, physiology, cellular structure, and metabolic pathways compared to other organisms, and development of fermentation methods and different bacterial culture conditions [46]. For this purpose, researchers have made significant efforts to produce recombinant proteins in *E. coli* using methods and techniques that minimize the time and cost required to produce the desired product. For the mass production of recombinant protein in *E. coli*, it is necessary to use a nutrient-rich culture medium. Generally, a specific culture medium is selected for cell culture because its nutrients can be controlled. The ability to produce recombinant protein on a large scale depends on two factors: biomass concentration and product production efficiency. Optimizing the composition and concentration of the growth medium, as well as environmental conditions, during the manufacturing process is a key strategy for increasing production efficiency. Although immunotoxins hold significant promise, other agents are also used in conjunction with them for therapeutic applications. Additional areas of interest for immunotoxins involve regulating immune responses, such as T cell suppression or depletion of regulatory T cells. The antiviral properties of immunotoxins, when tested on eukaryotic cells, have revealed new characteristics and functional domains of toxins [47].

4.3. The Importance of Bacterial-Source Immunotoxins

At first, protein toxins were primarily regarded as pathogenic factors produced by bacteria or toxins found in poisonous plants. However, years later, it was discovered that many of these toxins share similar biochemical mechanisms, such as the inhibition of protein synthesis. Diphtheria toxin and Pseudomonas exotoxin, for example, both ADP-ribosylate elongation factor 2 (EF-2), thereby disrupting protein synthesis during the elongation phase [48]. The A chain of ricin is an N-glycosidase and is toxic by depurinating a critical adenine in the S28 rRNA. Researchers have used these toxins to develop immunotoxins. In the early stages, three candidate toxins were considered: the plant toxin ricin (and similar toxins found in other plants), as well as diphtheria toxin and Pseudomonas exotoxin [49]. Factors that influence the selection of an appropriate immunotoxin include the toxin's structure, domain ori-

entation, expression and purification efficiency, ease of cloning, sugar linkages, immunogenicity, and potential for nonselective toxicity [50]. Each toxin contains a single enzymatically active domain and must reach the cytosol to kill the target cell effectively.

Additionally, each toxin has a binding domain that must be either removed or neutralized before it can bind to an antibody. Diphtheria toxin is transported from the acidic endosome to the cytosol by its T domain, whereas ricin and Pseudomonas exotoxin enter the rough endoplasmic reticulum before reaching the cytosol. Pseudomonas exotoxin has specific processing sequences that facilitate its transport to the endoplasmic reticulum. Both diphtheria toxin and Pseudomonas exotoxin undergo a single protease cleavage step, along with the reduction of a key disulfide bond. Thorpe et al. [51] demonstrated that protein toxins could be used to kill preselected cell types; however, their antibodies for producing immunotoxins had poor activity. Later, using the same approach and using monoclonal antibody technology, scientists produced immunotoxins with better specificity [52]. These immunotoxins were derived from ricin, diphtheria toxin, and Pseudomonas exotoxin.

4.4. Second and Third Generation Immunotoxins

When the toxin is bound to an antibody without its receptor region, it forms a second-generation immunotoxin. While a whole antibody, such as IgG, has a short half-life and performs well in vivo, its large size restricts its ability to penetrate tissues, particularly in the case of solid tumors. Additionally, most monoclonal antibodies used in first- and second-generation immunotoxins are derived from mice [53]. The use of nonhuman monoclonal antibodies presents particular challenges. However, advancements in molecular cloning, gene fusion (the joining of genetic segments in the lab), and prokaryotic expression systems have transformed the production of immunotoxins, leading to the development of third-generation immunotoxins [54]. A significant breakthrough in recombinant immunotoxin research was the expression of single-chain fragments (antibody variable regions) in *E. coli*, which retained their ability to bind antigens. This discovery paved the way for the creation of the first recombinant antibody-toxin fusion proteins [55].

Third-generation immunotoxins consist of antibody variable fragments linked to toxins that lack a binding domain. Over 1000 third-generation immunotoxins have been developed to date, with most targeting cancer cell-specific antigens [56]. While this approach to designing recombinant immunotoxins was promising, challenges arose in expressing and purifying active monomeric immunotoxins. Many of these challenges were addressed through techniques like codon optimization, inclusion body production, and various extraction methods. Antigens such as mesothelin, CD22, and CD25 are currently being tested in clinical trials for cancer therapy. Other antigens, such as HER2/neu, Lewis-Y, CD19, and CD30, were initially explored in preclinical studies but were later abandoned due to systemic toxicity or limited effectiveness against cancer cells [33]. Recent advancements in immunotoxin production have focused on creating smaller, less immunogenic versions of the 38/40 PE molecule. By removing most of the domain II region of PE, smaller molecules were developed that retained their cytotoxic properties while eliminating several immunogenic epitopes. This deletion of domain II in the PE toxin also removed lysosomal cleavage sites, resulting in the creation of a molecule known as LR (lysosomal resistance).

Types of immunotoxins based on *Pseudomonas* exotoxin include LMB-2 Anti-Immunotoxin, OVB3-PE, and LMB-2 25CD, which are third-generation. This immunotoxin consists of the variable VH and VL domains of murine 25CD-Anti, with the VL linked at the C-terminal end to 38PE by a linker called ASGGPE. 25CD is the alpha chain of the interleukin-2 receptor (IL-2R). IL-2R is overexpressed on cells in immune system disorders and hematological cancers. Phase I clinical trials for 2LMB-2 were finished in 2011. In this trial, conducted on patients with blood cancers, one patient achieved a complete response (cured) to the immunotoxin, and seven patients experienced a partial response. PE3-OVB immunotoxin consists of monoclonal antibodies [57]. 3OVB b2IgG is a murine 3OVB linked to the complete PE by a thiourea linkage. The 3OVB monoclonal antibody responds to various tumor cell lines. In a clinical study of ovarian cancer patients treated with the immunotoxin PE3-OVB, none of the patients responded to the treatment [58].

Concerning the attachment of toxins to cell-binding ligands, the initial candidate in the group of toxin-ligand molecules was EGF, followed by IL-6, IL-4, IL-2, IL-13, and TGF-α ligands. In the case of diphtheria toxin, MSH, TF, and IL-2 ligands were also used [59]. Toxin-ligands can kill cells via the corresponding receptor; however, the toxin-ligand molecule can also deliver various signals to cells. Many peptide receptors bind to surface receptors to send a growth or survival message. These signals are conveyed through phosphorylation cascades and occur rapidly. As a

result, the growth or survival signal from the toxin can reach the cell within hours. The toxin is then transported to the cytosol, where it interferes with protein synthesis. Despite these challenges, DT-IL2 remains the only approved immunotoxin in this group for treatment [60].

*Diphtheri*a toxin is a 535-amino-acid protein belonging to the ADP-ribosylating toxin family. It is the primary virulence factor of *Corynebacterium diphtheriae* (the causative agent of diphtheria) and shares functional similarities with Pseudomonas exotoxin. This immunotoxin is the only one approved by the US Food and Drug Administration and is a conjugate of two recombinant anti-CD3 antibodies (A-dmDT390-bisFv(UCHT1)) derived from the murine monoclonal antibody 3CD-Anti. In a study of six patients with 3CD-positive T-cell lymphoma, this immunotoxin was found to kill over 99% of normal T cells within two to three days. In drug-immunotoxin combinations, ammonium chloride has been used in conjunction with the ricin A immunotoxin to sensitize cultured cells further and enhance its efficacy [61].

Additionally, calcium channel inhibitors have been shown to boost the activity of Pseudomonas exotoxin-based immunotoxins. The concurrent use of endosome-disrupting adenovirus has also been shown to enhance the effects of Pseudomonas immunotoxins. However, none of these combinations have been tested in vivo due to challenges in achieving the necessary drug concentrations and concerns regarding their safety.

4.5. Bacterial Vaccines in Cancer Immunotherapy

Researchers have engineered probiotic bacteria that train the immune system to kill cancer cells, opening the door to a new class of cancer vaccines that harness the inherent tumor-targeting capabilities of bacteria. These microbial cancer vaccines could be tailored to target a person's specific primary tumor and metastases, potentially preventing future recurrences [62]. In studies involving mouse models of advanced colorectal cancer and melanoma, the bacterial vaccine deceived the immune system into suppressing, growing, or, in many cases, eliminating them [63]. All while leaving healthy parts of the body alone. The bacterial vaccine is significantly more effective than peptide-based cancer vaccines previously used in clinical trials [64]. One of the primary advantages of this approach is its ability to simultaneously activate and coordinate all components of the immune system, thereby triggering an antitumor immune response. Researchers believe this is why the system performs so well in advanced solid tumor models, which have traditionally been challenging to develop. The overall result is that the bacterial vaccine can control or eliminate the growth of both primary and metastatic tumors, leading to extended survival in mouse models. Since every cancer is unique, tumor cells carry distinct genetic mutations that differentiate them from normal, healthy cells. By programming bacteria to direct the immune system to target these specific mutations, more effective strategies can be engineered to stimulate the body's immune response. As researchers continue to enhance this approach through further genetic programming, they are approaching the stage where this treatment can be tested in human patients.

4.6. Using Bacteria for Cancer Therapy

Bacteria are still being utilized as a treatment for early-stage bladder cancer. Researchers have discovered that certain bacteria can naturally migrate to and colonize tumors, thriving in the low-oxygen environment typical of these areas, while locally stimulating an immune response. However, in this application, the bacteria typically cannot precisely guide the immune response to attack the cancer [65]. While these traits alone may not be powerful enough to prompt immune responses capable of eliminating tumors, they provide a strong foundation for developing new cancer therapies.

The new approach begins with a probiotic strain of *E. coli*. Researchers then genetically modify the bacteria to control how they interact with the immune system and train it to target cancer cells. These engineered bacteria carry specific cancer-related proteins, known as neoantigens, that are unique to the cancer being treated. These neoantigens prompt the immune system to recognize and attack cancer cells expressing the same proteins, leaving healthy cells unaffected.

Thanks to the bacterial system and additional genetic alterations, these therapies also target the immunosuppressive mechanisms that tumors use to evade immune detection. The modifications ensure that the bacteria's ability to evade immune attacks is suppressed. As a safety feature, the engineered bacteria are easily recognized and eliminated by the immune system, quickly clearing them from the body if no tumor is present. In mouse tests, researchers found that these genetically engineered bacterial cancer vaccines attracted various immune cells to at-

tack tumor cells while preventing immune responses that would usually suppress the attack. The vaccine slowed cancer growth in mice before tumors developed and prevented the recurrence of tumors in mice that had previously been treated, indicating potential for preventing cancer relapse in patients who have already undergone treatment.

The first step in creating these microbial vaccines for individual patients involves sequencing the patient's cancer to identify its unique neoantigens through bioinformatics. Next, the bacteria are engineered to produce large quantities of the specific neoantigens, along with other immune-boosting factors. When injected into the patient, the bacteria travel to the tumors, proliferate, and continuously produce and release the engineered therapeutic compounds. Once activated by the bacterial vaccine, the immune system is triggered to eliminate cancer cells throughout the body and prevent further spread. Since each tumor has its own unique set of neoantigens, the treatment is tailored to each patient. The timing of the therapy is initially based on the tumor's genetic sequence, so researchers only need to develop the bacterial strains—a process that can be accomplished quickly. These bacteria are simpler than some other vaccine platforms and are specifically designed to combat the tumor's ability to mutate and evade treatment rapidly. As the team leader explained, "The platform allows us to deliver numerous different neoantigens, making it theoretically difficult for tumor cells to evade all of these targets at once and escape immune detection." Researchers believe their approach may be more successful than previous cancer vaccines. While earlier vaccines may prompt immune responses to tumor neoantigens, they often fail to address the immunosuppressive tumor environment effectively. The bacteria in this system can deliver higher concentrations of therapeutic agents than traditional methods, with the ability to target the tumor specifically and better control how the immune system is activated.

4.7. New Anticancer Nano-Formulations Based on Cyanobacteria and Algae

Since the beginning of civilization, biologically active compounds derived from a wide range of algae and cyanobacteria have been widely utilized in various industrial and biomedical applications. Cyanobacteria and algae are important biological resources that contain a multitude of biomolecules, including polysaccharides, pigments, essential fatty acids, polyketides, vitamins, lectins, steroids, antioxidants, fibers, MAAs, proteins, and halogenated compounds [66]. These compounds are beneficial in the pharmaceutical, biomedical, and food-pharmaceutical fields due to their multifunctional applications. Our knowledge and awareness of algal metabolites have undoubtedly increased significantly over the past decade; however, many challenges remain in their application in the medical sector, as well as in terms of their nanoformulation and commercialization. Unveiling the enhanced anticancer mechanisms of nanoformulations containing algal secondary metabolites will help accelerate the development of marine drugs and nano-medicines. In the current context, the limited commercial development of drugs utilizing microalgae and their structurally diverse bioactive compounds, such as terpenes, alkaloids, steroids, polysaccharides, lipids, and polyphenols, is highlighted. More technologies are needed to explore the effectiveness and degree of efficacy of these anticancer secondary metabolites in the form of nanoformulations with nanoparticles. Nanofusion and green technologies should be integrated to explore these anticancer drug nanoformulations derived from cyanobacteria and microalgae [67]. A concept from start to finish is outlined to interest the reader in further research to achieve advanced innovation in commercial platforms. Scaling up commercialization, along with technological development, should also be a primary task for cost-effective nanoformulations of marine microalgae. Future research should focus on exploring the new functions and applications of micro-algal secondary metabolites. The remarkable advances made in the fields of materials engineering, pharmaceuticals, biology, chemistry, and medicine have led to significant improvements in nanotechnology achievements and the practical application of nanoparticles as powerful tools in various branches of human life. Nanoparticles with antibacterial activity are confidently used in food protection, antibacterial surfaces and textiles, new nano-medicines, dentistry, and other fields. Antibacterial nanoparticles include a wide range of materials, including metals, metal oxides, and nanoscale carriers. The antibacterial function of nanoscale carriers is realized by the release of active substances (i.e., metal ions or antibiotics) from the organic or inorganic matrix. The antibacterial action of nanoparticles is controlled by particle size, chemical composition, and immobilization. The sustained release of active ingredients into the environment is a key factor in the successful application of antibacterial nanoparticles. However, attention must be paid to the toxicity of nanoparticles and the safety of their application.

5. Limitations

Despite the high level of heterogeneity, which could substantially impact the reliability of meta-analysis estimates by increasing uncertainty and questioning the average effect, we were unable to conduct subgroup analyses because there were only a few studies included in each subgroup. The fact that there is considerable heterogeneity (I^2 > 75%) suggests that the effects of SDPP are likely to vary significantly across studies. This may be due to variations in the species, dose, or methodology used to evaluate the microbiota. The high heterogeneity observed in OTUs may stem more from technical inconsistencies in microbiome studies than actual biological differences induced by SDPP. Variability in OTU counts may reflect technical artefacts (e.g., sequencing depth) rather than biological effects.

6. Conclusions

Our meta-analysis suggests that SDPP affects gut microbiota diversity (e.g., it reduces the Shannon and Chao1 indices) and modulates immunological responses, likely by generating SCFAs and inhibiting TLR4 through the F/B ratio. Alternative immunomodulatory methods, such as vaccines, are effective only on specific pathways. SDPP possesses a polyclonal immunoglobulin profile and fortifies the gut barrier, rendering it a distinctive, broad-spectrum approach. Subsequent research should elucidate the optimal dosages and their interactions with other therapies. Although there were noticeable differences between studies and difficulties in replicating basic ecological measurements, the purpose of this analysis was to identify the consistent characteristics of the gut microbiota's response to the SDPP diet, in order to pinpoint specific areas for further mechanistic research. The results were obtained by analysing data from several laboratories. They provide a strong basis for future research aimed at understanding the connections between changes in microbial ecology, dietary consumption, and their effects on host health and disease. Like other drugs available for cancer treatment, immunotoxins come with mild side effects, including diarrhea, fever, and nausea. In some cases, these can be more severe, limiting the dosage that can be administered. A significant drawback of immunotoxins is their immunogenicity, which is triggered by their protein structure and results in an immune response within the body. The immune system produces antibodies against both the mouse antibody fragment and the protein toxin. As a result, when antibody levels against the immunotoxin rise, the patient can no longer continue treatment. To address this issue, a new generation of immunotoxins, composed of humanized or fully human antibody fragments, has been developed to reduce their immunogenicity. Another significant disadvantage is the potential for vascular leak syndrome, a serious condition that can be fatal. This syndrome occurs when immunotoxins are administered intravenously and interact with vascular epithelial cells. Hepatotoxicity is also a profound side effect associated with immunotoxins.

Author Contributions

Conceptualization, P.A., I.G.Q., and E.K.N.; formal analysis, P.A., I.G.Q., and E.K.N.; investigation, S.A.M., S.S.M., and W.N.; data curation, P.A., I.G.Q., and E.K.N.; writing—original draft preparation, P.A., I.G.Q., and E.K.N.; writing—review and editing, S.A.M., S.S.M., and W.N. All authors have read and agreed to the published version of the manuscript.

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