Review

Effects and Mechanisms of Probiotics, Prebiotics, Synbiotics, and Postbiotics on Metabolic Diseases Targeting Gut Microbiota: A Narrative Review

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Abstract: Metabolic diseases are serious threats to public health and related to gut microbiota. Probiotics, prebiotics, synbiotics, and postbiotics (PPSP) are powerful regulators of gut microbiota, thus possessing prospects for preventing metabolic diseases. Therefore, the effects and mechanisms of PPSP on metabolic diseases targeting gut microbiota are worth discussing and clarifying. Generally, PPSP benefit metabolic diseases management, especially obesity and type 2 diabetes mellitus. The underlying gut microbial-related mechanisms are mainly the modulation of gut microbiota composition, regulation of gut microbial metabolites, and improvement of intestinal barrier function. Moreover, clinical trials showed the benefits of PPSP on patients with metabolic diseases, while the clinical strategies for gestational diabetes mellitus, optimal formula of synbiotics and health benefits of postbiotics need further study. This review fully summarizes the relationship between probiotics, prebiotics, synbiotics, postbiotics, and metabolic diseases, presents promising results and the one in dispute, and especially attention is paid to illustrates potential mechanisms and clinical effects, which could contribute to the next research and development of PPSP.

Keywords: probiotics; prebiotics; synbiotics; postbiotics; gut microbiota; obesity; type 2 diabetes mellitus; gestational diabetes mellitus; metabolic diseases

1. Introduction

Metabolic syndrome is a cluster of metabolic disorders, manifested as dyslipidemia, hyperglycemia, insulin resistance, oxidative stress, inflammation, hypertension, and neurodegeneration, which is associated with metabolic diseases, such as obesity, diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and osteoarthritis [1,2]. Moreover, different metabolic diseases are often associated with each other, for example, obesity is a risk factor of type 2 diabetes mellitus and excess body weight also contributes to the development of NAFLD [3]. Recent studies have found out that the imbalance of gut microbiota is crucial to metabolic diseases [4,5]. Therefore, the regulation of gut microbiota could be a promising way out of this situation [6]. On the one hand, it is generally recognized that gut microbial homeostasis itself is a vital part of the whole metabolic system.
so that the regulation of beneficial and conditioned pathogenic bacteria is one of the most
direct mechanisms to improve metabolic function [7]. On the other hand, gut microbiota
continuously excretes bioactive molecules in the bowel lumen and some of them may
translocate into the circulation and further make an influence on the metabolic process
as specific ligands [8]. During the process, intestinal integrity plays an important role by
blocking the harmful bacterial metabolites transferred into the circulation [9].

Probiotics are a series of beneficial microorganisms, and prebiotics are traditionally
non-digestible food ingredients that selectively stimulate the growth and activity of a
limited number of bacteria in the digestive tract [10]. Recently, there is an emerging trend
to explore whether synbiotics (a combination of prebiotics and probiotics) and postbiotics
(inanimate microorganisms and/or their components that confers a health benefit on the
host) possess good biological activities for the prevention of metabolic diseases [11–13].
According to the results from experimental studies and clinical trials, probiotics, prebiotics,
synbiotics, and postbiotics (PPSP) have shown alleviated effects on obesity, type 2 diabetes
mellitus, and other metabolic diseases in most cases, but the situation could be uncertain
when the patients are during pregnancy [14]. In this review, we summarize the results from
recent studies (Web of Science within recent five years) to comprehensively exhibit the
bioactive effects, potential mechanisms, and clinical action of PPSP on metabolic diseases.

2. Bioactive Effects of Probiotics, Prebiotics, Synbiotics, and Postbiotics on
Metabolic Diseases

2.1. Obesity

Obesity is intimately related to gut microbiota, and probiotic strains possess beneficial
effects on attenuating obesity, such as Lactobacillus pentosus GSSK2 and Lactobacillus plantarum
GS26A [15]. Several studies showed that the anti-obesity effects of probiotics were different
between the lyophilized bacteria and alive bacteria, as well as the single-strain and multi-
strain [16,17]. Several studies highlighted that the lyophilized Lactobacillus casei IMVB-7280
possessed stronger anti-obesity property than lyophilized Bifidobacterium animalis VKB and
VKL strains [16]. Moreover, the alive multi-strains involving Acetobacter, Bifidobacterium,
Lactobacillus, and Propionibacterium could more effectively improve obesity, insulin resis-
tance, pro-inflammatory cytokines production, and adiponectin level when compared
with the lyophilized single-strain or multi-strains [18]. Besides, diverse evidence showed
that prebiotics (like polyphenols) could impact the progression of obesity via the regu-
lation of gut microbiota [19,20]. Owing to the promising application value of prebiotics
in the management of metabolic diseases, researchers keep modifying the strategies of
food processing to enhance the therapeutic effects [21,22]. For example, the anti-obesity
effect of resistant starch could be elevated after modifying with the amylosucrase from
Deinococcus geothermalis [23]. Moreover, synbiotics containing Bifidobacterium lactis, Lacto-
bacillus rhamnosu, and oligofructose-enriched inulin could more effectively regulate the
intestinal microenvironment than single components [10,24]. What’s more, an in vivo study
based on resveratrol-fed mice implied that postbiotics could be the reason why resveratrol
was beneficial to anti-obesity, but further clinical research was needed to provide more
reliable evidence [25].

2.2. Type 2 and Gestational Diabetes Mellitus

Fermented foods like yogurt were beneficial to type 2 diabetic patients, especially those
who were refractory to conventional therapy [26,27]. A prospective study on 8574 adults
suggested that yogurt consumption was inversely associated with the risk of type 2 diabetes
mellitus (hazard ratio (HR): 0.73; 95% confidence interval (CI): 0.61, 0.88) [28]. However,
the side effects of sugar-sweetened yogurt have caused concern [29]. Because of the
promising beneficial effects of probiotics on type 2 diabetes mellitus, researchers keep
optimizing the applicational strategy, for example, the utilization of the monk fruit extract
as a novel sweetener in yogurt could more effectively improve serum lipid level than
yogurt alone, and simultaneously avoid the health risk caused by sugar [30]. Moreover,
several prebiotic foods like *Lactobacillus plantarum*-fermented *Momordica charantia* juice possessed a better anti-diabetic effect than the native one [31]. Furthermore, because the treatment of type 2 diabetes mellitus is often accompanied by the regulation of gut bacterial metabolites, postbiotics could be an alternative therapeutic agent for probiotics, prebiotics, and fecal microbiota transplant [32]. However, other studies implied that the consumption of symbiotic foods only revealed limited mitigation in diabetes mellitus, especially gestational diabetes mellitus [33, 34]. For example, adding extra fish oil into probiotic supplements containing *Bifidobacterium lactis* and *Lactobacillus rhamnosus* HN001 failed to reduce the risk of gestational diabetes mellitus whether combined as symbiotics or used as single agents [35].

### 2.3. Other Metabolic Diseases

The utilization of probiotics has been recognized as a potential treatment for other metabolic diseases like NAFLD [36]. Moreover, a cross-sectional study with 26,016 subjects reported that the intake of prebiotics, such as dietary fiber, phytochemicals, and complex carbohydrates, was inversely associated with the risk of metabolic disorders [37]. Furthermore, gut microbiota played a role in metabolic-related diseases especially when accompanied by low-grade chronic inflammation [38–40]. Prebiotics like polysaccharides from *Cyclocarya paliurus* could improve metabolic function and chronic inflammation by increasing *Bacteroidetes* abundance and downregulating Toll-like receptor-4-mitogen-activated protein kinase (TLR4-MAPK) signaling pathway [41]. However, the abundances of *Bacteroides* and *Parabacteroides* were decreased in obese mice with low-grade inflammation after receiving unsaturated alginate oligosaccharides [42]. Besides, the oral administration of glucose solution with probiotics could improve intestinal barrier function and inflammation in patients after colorectal cancer surgery [43]. Several studies highlighted that the synergistic effects of probiotics and prebiotics on dyslipidemia and hypercholesterolemia remained a mystery [44]. The co-administration of probiotics and natural prebiotic food like *Agaricus bisporus* mushroom revealed the same curative effect on dyslipidemia as each agent alone [44]. Likely, the combination of probiotics (*Lactobacillus acidophilus* La-5) and prebiotics (inulin oligofructose) did not show a better therapeutic effect on metabolic-related diseases compared with the prebiotics or probiotics alone [45].

In short, PPS could alleviate metabolic diseases, and the co-intervention of multiple alive bacteria strains could be a promising way of probiotics application. Moreover, the enzyme-modification and probiotic-fermentation could effectively enhance the benefits of prebiotics. Furthermore, the effects of *Bacteroidetes* in metabolic diseases accompanied with low-grade inflammation need further investigation.

### 3. Mechanisms of Probiotics, Prebiotics, Synbiotics, and Postbiotics on Metabolic Diseases by Targeting Gut Microbiota

The intervention of probiotics (like *Bifidobacterium* and *Lactobacillus*), prebiotics (like inulin oligofructose and other polysaccharides), synbiotics (consist of probiotic strains and prebiotic foods), and postbiotics (like short-chain fatty acids (SCFAs) and muramyl dipeptide) could make an important influence on metabolic function. The recent studies showed that the modulation of gut microbiota composition, regulation of gut microbial metabolites, as well as improvement of the intestinal barrier function were three major mechanisms of PPS on regulating metabolic diseases, which would be discussed below.

#### 3.1. The Modulation of Gut Microbiota Composition

Probiotics have been proposed as a suitable strategy for preventing metabolic diseases [46]. The mixture of probiotics containing *Bifidobacterium lactis* LMG P-28149 and *Lactobacillus rhamnosus* LMG S-28148 could modulation the composition of obesity-related gut microbiota and restore *Akkermansia muciniphila* and *Rikenellaceae* abundances while reducing *Lactobacillaceae* abundance [47]. Besides, other metabolic-related diseases like inflammatory bowel disease were associated with digestive system dysfunction and gut microbiota dysbiosis, manifested as the less abundances of *Bifidobacteria* and *Lactobacillus*, as
well as a higher abundance of *Escherichia coli* [48]. Moreover, gut microbiota is considered as a trigger for the metabolic inflammation in obesity and type 2 diabetes mellitus, and the administration of *Lactobacillus reuteri* could improve metabolic function by inhibiting the growth of harmful bacteria (like *Yersinia enterocolitica*) and improving tetrathionate metabolism in TLR1-deficient mice with intestinal inflammation [49,50]. Furthermore, the intake of *Lactobacillus casei* could prevent metabolic-related hypertension in perinatal rats by decreasing the *Firmicutes* to *Bacteroidetes* ratio and the expression of angiotensin-converting enzyme (ACE), while increasing *Akkermansia* and *Lactobacillus* abundances [51]. In addition, an in vivo study with male Swiss albino mice reported that the probiotic-fermented milk containing *Lactobacillus reuteri* LR6 could improve protein-energy malnutrition and immunological function in mice with increasing *Bifidobacteria*, *Firmicutes*, and *Lactobacilli* abundances [52].

The healthy influence of gut microbiota was started on the early stage of life, and the experimental studies showed that prebiotic dextrin from maize starch and lentil-based diet could promote the growth of *Actinobacteria* and *Bacteroidetes*, while decrease *Firmicutes* abundance, thus might be beneficial to overweight and obese children [53–55]. Moreover, resistant dextrin from wheat and corn starch could improve lipid and glucose metabolism in insulin resistance mice by increasing *Akkermansia* and *Prevotella* abundances, followed by upregulating the insulin receptor substrate 1 (IRS1)-protein kinase B (Akt)-glucose transporter 2 (GLUT2) signaling pathway as well as upregulating the sirtuin 1 (SIRT1)-adenosine monophosphate kinase (AMPK)-peroxisome proliferators activated receptor α (PPARα)-carnitine palmitoyltransferase 1α (CPT1α) signaling pathway [56]. Furthermore, the supplementation of whole garlic improved serum lipid profile, liver function, and insulin resistance in dyslipidemia mice, with increasing *Lachnospiraceae* while reducing *Prevotella* abundances [57]. Inulin was a common prebiotic, and the in vivo studies showed that the intake of inulin oligofructose improved obesity, glycemic dysregulations, and the blood-brain-barrier integrity, with decreasing the *Firmicutes* to *Bacteroidetes* ratio while increasing *Bifidobacterium* abundance [58,59]. Additionally, the pregnant rats which received oligofructose had a lower obesity risk in their offspring, with higher abundances of *Bifidobacterium* and *Collinsella* [60]. Besides, fucoidan polysaccharides could improve gut microbial diversity with increasing the abundance of *Bacteroidetes* and *Propionibacteria*, enhancing the bile salt hydrolase activity of *Lactobacillus casei* DM8121, as well as upregulating the expression of hepatic cholesterol 7-α hydroxylase, while the abundances of *Actinobacteria* and *Firmicutes* were decreased [61,62].

Synbiotics were considered as a new frontier in obesity prevention, and the omega-3 fatty acids with a mixture of alive probiotics containing *Bifidobacterium*, *Lactobacillus*, and *Propionibacterium* showed a more pronounced reduction in hepatic steatosis and lipid accumulation compared to probiotics alone [63,64]. Moreover, the oral supplements of combined *Bacillus licheniformis* and xylo-oligosaccharides could more effectively improve body weight gain and lipid metabolism in obese rats with decreasing the abundances of *Desulfovibrionaceae* and *Ruminococcaceae* [65]. In addition, a mixture of *Lactobacillus plantarum* PMO 08 with chia seeds revealed a synergistic anti-obesity effect on obese mice, and led to a more favorable intestinal microenvironment for *Lactobacillus plantarum* growth [66].

Butyrate was a typical postbiotics produced from gut microbiota, and it could alleviate intestinal inflammation induce by *Citrobacter rodentium*, and result in increasing *Lachnospiraceae* and *Proteobacteria* as well as decreasing *Clostridiaceae* abundances in mice [67]. Moreover, butyrate administration could ameliorate NAFLD and increase the abundances of butyric-produced bacteria such as *Blautia*, *Christensenellaceae*, and *Lactobacillus* in return [68]. So, there could be a bi-directional regulation and positive feedback action between the supplement of postbiotics like butyrate and the growth of related bacteria [69].

In general, PPSP could regulate metabolic diseases by regulating the abundances of *Akkermansia*, *Bacteroidetes*, *Blautia*, *Bifidobacteria*, *Bifidobacterium*, *Collinsella*, *Christensenellaceae*, *Desulfovibrionaceae*, *Lachnospiraceae*, *Lactobacillus*, *Proteobacteria*, *Rikenellaceae*, and *Ruminococcaceae*, while decreasing the abundances of *Clostridiaceae*, *Firmicutes*, *Lactobacilli*...
laceae, and Yersinia (Figure 1). Meanwhile, the modulation of gut bacteria composition was accompanied by upregulating IRS1-Akt-GLUT2 and SIRT1-AMPK-PPARα-CPR1α signaling pathways while downregulating the mRNA expression of ACE, as well as improving tetrathionate metabolism, bile salt hydrolase activity, and hepatic cholesterol 7-alpha hydroxylase expression (Table 1).

Figure 1. Mechanisms of PPSP on metabolic diseases targeting gut microbiota. PPSP directly alleviate metabolic diseases by regulating the abundances of beneficial and harmful bacteria. Besides, PPSP indirectly ameliorate metabolic diseases by promoting the production of acetate, propionate, butyrate, isovalerate, lactic acid, and palmitoylthanolamide, while suppressing the production of LPS, TMAO and reducing the bile acid pools. Moreover, the improvement of intestinal barrier function played an important role in attenuating metabolic diseases, with upregulating claudin 1, GLP1, IL-10, occludin 1, and ZO-1 expressions. These mechanisms collectively improve the whole metabolic system by targeting several pivotal molecular, such as upregulating IRS1-Akt-GLUT2, SIRT1-AMPK-PPARα-CPR1α, TLR2-PPARγ-AMPK, and NOD-IRF4 signaling pathways. Abbreviation: ACC, acetyl-CoA carboxylase; Akt, protein kinase B; AMPK, adenosine monophosphate kinase; CPR1α, carnitine palmitoyltransferase 1α; GLUT2, glucose transporter 2; IRF4, interferon regulatory factor 4; IRS1, insulin receptor substrate 1; LPS, lipopolysaccharide; NOD2, oligomerization domain-containing protein 2; PPARα/γ, peroxisome proliferators activated receptor α/γ; SIRT1, sirtuin 1; TLR2, Toll-like receptor 2; TMAO, trimethylamine-n-oxide; ZO-1, zonula occludens-1.
Table 1. The effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases from experimental studies.

| Supplements                        | Models                        | Doses                  | Target Disease                                | Main Effects and Mechanisms                                                                 | Ref. |
|------------------------------------|-------------------------------|------------------------|------------------------------------------------|---------------------------------------------------------------------------------------------|------|
| **Probiotics**                     |                               |                        |                                                |                                              |      |
| *Bifidobacterium lactis* LMG P-28149, and Lactobacillus rhamnosus LMG S-28148 | in vitro, in vivo            | 10⁸ CFU                | Obesity and insulin resistance                | Restoring Akkermansia muciniphila and Bifidobacterium; Upregulating PPARγ and lipoprotein lipase expression; Enhancing insulin sensitivity and TG clearance | [47] |
| *Bifidobacterium longum* PT10 and Lactococcus salivarius PT12 | in vitro, in vivo            | 5 × 10⁴ CFU             | Obesity                                         | Upregulating GLP1 and IL-10 expression.                                                        | [70] |
| *Lactobacillus plantarum* NK3 and *Bifidobacterium longum* NK3 | in vivo                       | 1 × 10⁹ CFU             | Obesity and osteoporosis                        | Improving intestinal barrier; Suppressing LPS production; Downregulating NF-κB-linked TNF-α expression; Improving intestinal barrier. | [71] |
| *Lactobacillus fermentum* MCC2760 | in vivo                       | 10⁶ CFU                 | Type 2 diabetes mellitus                        | Upregulating GLUT4, GLP1, and ZO-1 expression; Increasing Akkermansia and Lactobacillus.       | [72] |
| *Lactobacillus casei*              | in vivo                       | 2 × 10⁹ CFU             | Hypertension                                    | Decreasing Firmicutes to Bacteroidetes ratio and ACE expression.                              | [51] |
| *Bifidobacterium breve CECT7263* and *Lactobacillus fermentum* CECT5716 | in vivo                       | 10⁹ CFU                 | Hypertension                                    | Increasing butyrate-related bacteria; Elevating the plasma level of butyrate.                | [73] |
| *Lactobacillus johnsonii* and *Lactobacillus reuteri*         | in vivo                       | 10⁹ CFU                 | Inflammatory bowel disease and Osteoporosis     | Reducing LPS production; Improving tetrahexionate metabolism.                                | [49] |
| *Lactobacillus paracasei*           | in vivo                       | 0.8–1.2 × 10⁷ CFU       | Colitis with metabolic disorder                 | Increasing *Bifidobacteria, Firmicutes*, and *Lactobacilli*.                                   | [74] |
| *Lactobacillus reuteri* LR6         | in vivo                       | 1 × 10⁸ CFU             | Protein-energy malnutrition                     |                                              | [52] |
| **Prebiotics**                     |                               |                        |                                                |                                              |      |
| Matte starch dextrin and Lentil     | in vitro, in vivo             | 70.8% red lentil diet   | Obesity                                         | Increasing *Enterobacteria*; Decreasing *Bifidobacteria*.                                    | [53,54]|
| Inulin oligofructose               | in vivo                       | 5% in diet, 0.6 g/day   | Obesity                                         | Decreasing Firmicutes to Bacteroidetes; Increasing *Bifidobacteria*.                          | [58,59]|
| Chicory oligofructose              | in vivo                       | 10% in diet             | Obesity                                         | Increasing *Bifidobacterium* and *Collinsella*.                                               | [60] |
| Amylosucrase-modified chestnut starch | in vivo                       | 1500 mg/kg             | Obesity                                         | Upregulating SCFA-SCFRG3-mediated pathway.                                                     | [23] |
| Fuji FF                            | in vivo                       | 10% in diet             | Obesity                                         | Increasing acetic, propionic, and butyric acids production.                                    | [75] |
| Unsaturated alginic oligosaccharides | in vivo                       | 400 mg/kg              | Obesity                                         | Upregulating ZO-1 and occludin expression.                                                      | [42] |
| Acorn and sago polyosaccharides    | in vitro, in vivo             | 1% rs/c, 5% in diet     | Obesity and type 2 diabetes mellitus            | Reducing gut hyperpermeability and mucosal inflammatory biomarkers.                            | [62] |
| Galacto-oligosaccharides            | in vivo                       | 7% w/w                  | Obesity and Insulin resistance                  | Increasing GLP1 expression; Decreasing focal bile acid excretion.                              | [76] |
| Resistant dextrin from wheat and corn starch | in vivo                       | 5 g/kg                  | Type 2 diabetes mellitus                        | Increasing Akkermansia and Prevotella abundances; Upregulating IRS1-Akt-GLUT2 and SIRT1-AMPK-PPARα-CPR1α pathways; Increasing acetic and butyric acids production. | [56] |
| Isomaltodextrin                     | in vivo                       | 1, 2.5, 5% in drinking water | Insulin resistance                              | Improving intestinal barrier; Reducing circulation endotoxin level.                             | [38] |
| Whole garlic                       | in vivo                       | 5% in diet              | Dyslipidemia                                     | Increasing Lachnospiraceae; Decreasing Propionibacteria; Increasing *Bifidobacteria*, Propionibacteria, and the bile salt hydrolase activity of *Lactobacillus casei* DMH121. | [57,61]|
| Fucoidan and Galacto-oligosaccharides | in vitro, in vivo             | 100, 800 mg/kg         | Dyslipidemia                                     | Decreasing *Akkermansia* and *Firmicutes*. Regulating bile acids and tryptophan–serotonin metabolic pathways. | [77] |
| Oat and rye brans dietary fiber    | in vivo                       | 10% in diet             | Metabolic disorder                              |                                              |      |
Table 1. Cont.

| Supplements | Models | Doses | Target Disease | Main Effects and Mechanisms | Ref. |
|-------------|--------|-------|----------------|----------------------------|------|
| Agave salmiana fructan plus corn bran | in vivo | 10% in diet | Metabolic disorder | Increasing lactic acid production. | [78] |
| Glycolipids from tilapia heads | in vivo | 30 mg/kg | Colitis with metabolic disorder | Increasing Akkermansia, Allibaculum, Bifidobacterium, Coprococcus, Oscillinspora, and Prevotellaceae. Decreasing the fecal levels of acetate and propionate, and the plasma level of TMAO. | [79] |
| Long-chain inulin plus xylo-oligosaccharides | in vivo | 2.5 mL/kg | Obesity | Revealing positively synergistic effect on reducing hepatic steatosis and lipid accumulation compared to probiotics alone. | [63,64] |
| Syntotics | Bifidobacterium, Lactobacillus, Propionibacterium plus omega-3 fatty acids | in vivo | 7.5 × 10⁶ CFU/mL and 2 g/mL | Obesity | Decreasing Desulfovibrioaceae and Ruminococcaceae Revealing positively synergistic effect on improving body weight gain and lipid metabolism. | [65] |
| Bifidobacterium lactis, Lactobacillus plantarum | in vivo | 1 × 10⁷ CFU/mL and 4% in diet | Obesity | Decreasing Desulfovibrioaceae and Ruminococcaceae Revealing positively synergistic effect on improving obesity. | [66] |
| Lactobacillus paracasei N1115 plus xylo-oligosaccharides | in vivo | 1 × 10⁸ CFU and 10% in PBS | Obesity | Decreasing Firmicutes to Bacteroidetes ratio and Enterobacteriaceae Decreasing LPS production. | [81] |
| Clostridium butyricum plus corn bran | in vivo | 1 × 10⁸ CFU/g and 5% in diet | Intestinal impairment with metabolic disorder | Decreasing TLR4 and NF-κB expression. | [91] |
| Lactobacillus paracasei DSM 4633, plus oat b-glucon | in vivo | 2.2 × 10⁸ CFU/mL and 4 g/kg/day | NAFLD | Uregulating p38 MAPK pathway and the expression of occludin 1 and claudin 1. | [82] |
| Bifidobacterium bifidum V, Lactobacillus plantarum X plus Salvia miltiorrhiza polysaccharide | in vivo | 1-2 × 10⁶ CFU and 50 mg/kg | NAFLD | Allieving hepatic steatosis and insulin resistance improvement. | [83] |
| Clostridium butyricum plus corn bran | in vitro, in vivo | 100 µM and 500 mg/kg | Obesity | Decreasing LPS level. | [84] |
| Postbiotics | Exopolysaccharide from Lactobacillus plantarum L-14 | in vitro, in vivo | 100 µM and 500 mg/kg | Obesity | Decreasing pathogen abundances. | [85] |
| Muramyl dipeptide | in vivo | 100 µg | Obesity | Uregulating TLR2-AMPK pathway. | [86,87] |
| Butyrate | in vivo | 200 mg/kg | Type 2 diabetes mellitus | Uregulating NOD2-IRF4 pathway. | [88] |
| Butyrate | in vivo | 5% in diet | Type 2 diabetes mellitus | Increasing Lachnospiraceae and Proteobacteria. | [89] |
| Butyrate | in vivo | 140 mM | Metabolic disorder | Decreasing Clostridaceae. | [67] |
| Butyrate | in vivo | 200 mg/kg | NAFLD | Increasing Blautia, Christensenellaceae, and Lactobacillus. | [68] |
| Butyrate | in vivo | 0.6 g/kg | NAFLD | Increasing ZO-1 expression. | [90] |
| Long-chain polyolipate from Lactobacillus brevis | in vivo | 0.05 µg/µL | Colitis with metabolic disorder | Decreasing the levels of endotoxin. | [91] |

Abbreviation: ACE, angiotensin-converting enzyme; Akt, protein kinase B; AMPK, adenosine monophosphate kinase; CPR1, carnitine palmitoyl transferase 1α; ERK, extracellular regulated protein kinases; GLP1, glucagon-like peptide 1; GPR, G-protein coupled receptor; IL-10, interleukin-10; IRF4, interferon regulatory factor 4; IRS1, insulin receptor substrate 1; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NLCR3, nucleotide-binding oligomerization domain-like receptors 3; NOD2, nucleotide-binding oligomerization domain-containing protein 2; p38 MAPK, p38 mitogen-activated protein kinase; PPARα/γ, peroxisome proliferators activated receptor α/γ; SCFA, short-chain fatty acids; SIRT1, sirtuin 1; TLR2/4, TG, triglycerides; Toll-like receptor 2/4; TMAO, trimethylamine-n-oxide; TNF-α, tumor necrosis factor α; TRAF6, TNF receptor-associated factor 6; ZO-1, zonula occludens-1.

3.2. The Regulation of Gut Microbial Metabolites

Several gut microbial metabolites could indirectly influence host metabolism by interacting with several key steps involved in metabolic-related signaling pathways, such as G-protein coupled receptor (GPR), AMPK, and PPARγ [92,93]. The in vitro study showed that the mixture of Bifidobacterium lactis and Lactobacillus salivarius could promote the production of butyrate and propionate in the fermentation system [47]. Moreover, after comparing 23 bacteria strains, an experimental study revealed that Bifidobacterium longum PI10
and *Ligilactobacillus salivarius* PI2 could restrict lipid accumulation in adipocytes [70]. Furthermore, the *Lactobacillus plantarum* NK3 and *Bifidobacterium longum* NK49 could mitigate obesity and osteoporosis in mice by suppressing the production of lipopolysaccharide (LPS) from gut microbiota and downregulating nuclear factor kappa B (NF-κB)-linked tumor necrosis factor α (TNF-α) expression [71]. Additionally, probiotics containing *Bifidobacterium breve* CECT7263 and *Lactobacillus fermentum* CECT5716 ameliorated metabolic-related hypertension in rats by increasing the abundance of butyrate-related bacteria, and elevating the level of butyrate in plasma while reducing the production of LPS [73]. What’s more, the engineered *Lactobacillus paracasei* could produce metabolites like palmitoylethanolamide to maintain normal intestinal function in mice [74].

The intake of prebiotics could regulate the production of gut microbial metabolites like SCFAs and bile acids thus influencing the metabolic process [94]. It has been reported that the administration of isomaltoextrin was positively related to the concentrations of acetic and butyric acids in mice with glucometabolic disorder [38]. Moreover, an in vivo study revealed that the intervention of dietary fiber from oat and rye brans improved body weight, glucose metabolism, hepatic inflammation, and SCFAs production in mice, accompanied with regulating bile acids and tryptophan-serotonin metabolism [77]. Furthermore, the amylosucrase-modified chestnut starch could ameliorate obesity in mice by upregulating the SCFAs-GPR43-mediated signaling pathway [23]. Besides, inulin and fructan from *Agave salmiana* could be beneficial to prevent metabolic syndrome and related hypertension by regulating gut microbial metabolites, manifested as increasing the levels of acetic, propionic, butyric, and lactic acids while decreasing the level of trimethylamine-n-oxide (TMAO) [51,75,78]. In addition, galacto-oligosaccharides could inhibit the progression of obesity and insulin resistance in mice with increasing intestinal glucagon-like peptide 1 (GLP1) expression while decreasing fecal bile acid excretion [76].

The symbiotic intervention also revealed regulatory function in gut microbial metabolites production, and the combination of *Bifidobacterium lactis*, *Lactobacillus paracasei* DSM 4633, and oat β-glucan could inhibit body weight gain and metabolic complications in obese mice with restoring the fecal levels of acetate, propionate, and butyrate, as well as reducing the bile acid pools [80]. Besides, symbiotics containing *Clostridium butyricum* and corn bran could decrease the abundances of pathogens while promoting the growth of acetate-produced bacteria, which further lead to an increase of acetate and isovalerate [84]. Moreover, symbiotics containing *Lactobacillus paracasei* N1115 and fructo-oligosaccharides alleviated NAFLD in mice, resulting in improving lipid metabolism with inhibiting the production of LPS, as well as downregulating related molecular targets like TLR4 and NF-κB [82]. Furthermore, the symbiotics containing *Bifidobacterium bifidum*, *Lactobacillus plantarum* X, and polysaccharide from *Salvia miltiorrhiza* revealed a better beneficial effect on improving NAFLD and inhibiting LPS production than the single agent [83].

The postbiotics like exopolysaccharide from *Lactobacillus plantarum* L-14 could inhibit the differentiation of immature cells into mature adipocytes, as well as control body weight gain and lipid profiles in mice by upregulating the TLR2-AMPK signaling pathway [85]. Besides, the long-chain polyphosphate from *Lactobacillus brevis* could improve intestinal inflammation and intestinal barrier function by activating the extracellular regulated protein kinases (ERK) signaling pathway [91]. Additionally, the muramyl dipeptide from bacterial cell wall was a beneficial postbiotic which could mitigate obesity-induced insulin resistance by targeting nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and interferon regulatory factor 4 (IRF4) [86]. Further study showed that the interaction between postbiotics (like muropeptide) and NOD2 could improve insulin sensitization and inflammation, but the connection with NOD1 could worsen metabolic disorders [86,87].

In short, PPSP could regulate metabolic diseases by promoting the production of beneficial bacterial metabolites, such as acetate, propionate, butyrate, isovalerate, lactic acid, and palmitoylethanolamide. PPSP also restricted the production of LPS and TMAO, as well as reduced bile acid pools (Figure 1). Moreover, PPSP lead to upregulating AMPK, ERK, GPR43, IRF4, NOD2, and TLR2-mediated signaling pathways, as well as improving
tryptophan-serotonin metabolic pathways while downregulating TLR4, NF-κB, NOD1, and TNF-α-related signaling pathways (Table 1).

3.3. The Improvement of Intestinal Barrier Function

Intestinal barrier function, also called intestinal integrity, was strongly influenced by gut microbiota [95]. The oral administration of probiotics like *Bifidobacterium longum* NK49 and *Lactobacillus plantarum* NK3 could improve obesity and osteoporosis in mice by completing intestinal barrier integrity and further modulating immune cells with reducing TNF-α expression [71]. Besides, the single administration of *Lactobacillus fermentum* MCC2759 and MCC2760 was both beneficial to diabetic rats, but the MCC2760 strain showed a slightly better improvement in the intestinal barrier and the expression of GLUT4, GLP1, and zonula occludens-1 (ZO-1) than the MCC2759 strain [72]. Moreover, *Bifidobacterium longum* P110 was a highly potent inducer for GLP1 and interleukin-10 (IL-10), which could strengthen the intestinal barrier [70].

Prebiotics like isomaltodextrin possessed beneficial properties on chronic inflammatory-related insulin resistance by recovering intestinal barrier with reducing endotoxin level in circulation [38]. Likely, the polysaccharides from acorn and sago could reduce gut hyperpermeability and mucosal inflammatory biomarkers in obese and type 2 diabetic mice [62]. Moreover, unsaturated alginate oligosaccharides intervention improved the intestinal barrier in obese mice due to the increase of ZO-1 and occludin expressions [42]. Furthermore, the glycolipids from tilapia heads selectively increased the enrichment of intestinal barrier-related gut microbiota, such as *Akkermansia*, *Allobaculum*, *Bifidobacterium*, *Coprococcus*, *Oscillospira*, and *Prevotellaceae* in metabolic-related colitis mice, and consequently benefited the whole metabolic system [79].

An unhealthy diet could promote the growth of LPS-produced bacteria like *Enterobacteriaceae*, lead to the translocation of LPS via the impaired intestinal barrier, and further induce dyslipidemia, insulin resistance, systemic inflammation, and immune response [96,97]. An in vivo study revealed that the administration of synbiotics containing *Lactobacillus paracasei* HII01 and xylo-oligosaccharides could improve metabolic disorder and intestinal barrier in obese rats with avoiding metabolic endotoxemia and decreasing *Firmicutes* to *Bacteroidetes* ratio and *Enterobacteriaceae* abundance [81]. Moreover, synbiotics containing *Lactobacillus paracasei* N1115 and fructo-oligosaccharides could alleviate hepatic steatosis, cirrhosis progression, and intestinal barrier in mice with NAFLD, result in improving lipid profiles, fasting blood glucose, insulin, and TNF-α by upregulating p38 MAPK pathway and the expression of tight junction proteins (like occludin 1 and claudin 1) [82].

Postbiotics also have the potential to regulate gut barrier status and could improve metabolic diseases [98]. The intestinal barrier dysfunction was related to gut microbiota dysbiosis and chronic inflammation in type 2 diabetes mellitus, and the nucleotide-binding oligomerization domain-like receptors (NLRs) played a role in the inflammatory impairment [88]. The in vitro study of colonic epithelial cells showed that the over-expression of NLRC3 potentially benefited colonic epithelial barrier integrity due to the increase of TNF receptor-associated factor 6 (TRAF6)-mediated ZO-1 and occludin expression, and butyrate could improve the intestinal barrier in type 2 diabetic mice by upregulating GPR43 expression and stimulating NLRC3 in a TRAF6-dependent manner [88]. Besides, butyrate could restore intestinal barrier function in NAFLD mice with increasing ZO-1 expression in the small intestine and decreasing the levels of gut endotoxin in serum and liver [68,90]. Another in vivo study revealed that diet supplementation with butyrate mitigated metabolic disorder and intestinal epithelial impairment in type 2 diabetic mice by promoting the secretion of insulin without compensatory hyperplasia in pancreatic β cells [89]. It should be pointed out that gut microbiota and their metabolites could drive the development of insulin resistance in obesity and T2D, possibly by initiating an inflammatory response, which has been well reviewed by a recently published paper [50].

In summary, PPSP could alleviate metabolic diseases by improving intestinal barrier function with upregulating GLUT4, GPR43, NLRC3, p38 MAPK, TRAF6-mediated
signaling pathways and the expressions of claudin 1, GLP1, IL-10, occludin 1, and ZO-1 (Figure 1). PPSP could also regulate Allobaculum, Akkermansia, Bifidobacterium, Coprococcus, Enterobacteria, Lactobacilli, Oscillospira, and Prevotellaceae abundances, as well as reduce TNF-α expression and circulation endotoxin (Table 1).

4. Clinical Effects of Probiotics, Prebiotics, Synbiotics, and Postbiotics on Metabolic Diseases

Several clinical trials have focused on verifying the effects of PPSP on metabolic diseases, which would be discussed below.

4.1. Obesity

A 45-day clinical trial on 51 obese patients showed that the daily intake of fermented milk containing $2.72 \times 10^{10}$ CFU of Bifidobacterium lactis could improve blood lipids and inflammatory biomarkers like TNF-α and IL-6 [99]. Moreover, a 3-week intake of probiotics containing 9 probiotic strains included Bifidobacterium animalis SGB06, Bifidobacterium bifidum SGB02, Lactobacillus acidophilus SGL11, Lactobacillus delbrueckii DSM 20081, Lactococcus lactis SGL01, Lactobacillus plantarum SGL07, Lactobacillus reuteri SGL01, Streptococcus thermophiles, and Streptococcus thermophilus (1.5 × 10$^{10}$ colony-forming units (CFU) for each) could modulate body composition, gut bacterial composition, and psychopathological status among 60 obese and pre-obese women [100]. In addition, the identification of gut microbial enterotypes could be a crucial factor for obesity management because the prevalence of obesity is lower in people with Bacteroides or Prevotella enterotypes [101]. Furthermore, the consumption of probiotics containing Bifidobacterium breve CBT BR3 and Lactobacillus plantarum CBT LP3 could more effectively improve clinical biomarkers among obese patients with the Prevotella-rich enterotype than the Bacteroides-rich enterotype [102]. Additionally, a systematic review of 20 meta-analyses involving 16,676 adults showed a moderate effect of probiotics on body weight in overweight/obesity, and the authors also point out that because these products could not be without side effects for all persons, the risk-benefit assessment should be done before their prescription [103]. In fact, some side effects of probiotics have been reported, for example, Bifidobacterium and Lactobacillus could cause infections in extremely rare cases for pregnant women and neonate because the subjects are immunocompromised, and one obese patient had mild dyspepsia and diarrhea during a 12-week probiotic intervention [102]. It should be pointed out that diet is the most important factor shaping gut microbiota, and the effect of probiotics intervention is also affected by many other factors, such as unique host and microbiome features [104]. In the further, we will enter an era of precision medicine, and will require the development of new personalized probiotic approaches.

The intake of prebiotic foods has been recognized as a potential treatment for obesity [105]. The clinical trials showed that the daily intake of yacon (a natural source of phenolic compounds and fructo-oligosaccharides) at a dose of 25 g for 6 weeks could increase the plasma antioxidant capacity, while decrease oxidative stress and fecal SCFAs levels in obese patients with no severe side effects [106,107]. Moreover, a clinical trial on 42 overweight and obese children showed that the consumption of oligofructose-enriched inulin at doses of 8 g/day for 16 weeks reduced energy intake by regulating appetite [108]. Furthermore, the daily intake of 21 g oligofructose for 12 weeks could ameliorate metabolic endotoxemia and decrease the level of plasminogen activator inhibitor 1 (PAI1) among 37 obesity patients [109]. Additionally, a 12-week clinical trial with 125 overweight or obese adults showed that both inulin-type fructan and whey protein could benefit appetite management but just fructan increased Bifidobacterium abundance [110].

The growing up milk is fortified milk with extra synbiotics specifically designed for children aged from 1 to 2 years old, and it could decrease the percentage of body fat with 160 children after 12 months of consumption [111]. Besides, the intake of synbiotics containing 7 freeze-dried strains (Bifidobacterium breve, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus rhamnosus, and Streptococcus thermophiles, $10^9$ CFU/g for each) and 35 mg fructo-oligosaccharides could improve serum
insulin level and insulin resistance with 76 obese breast cancer survivors [112,113]. Additionally, the anti-obesity effects of synbiotics were inconsistent in some trials [114,115]. A clinical trial with 59 obesity patients reported that the daily intake of 500 mg synbiotics containing *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei* (2 × 10⁶ CFU/g for each) and 0.8 g inulin for 8 weeks improved lipid profiles and psychological status, without benefiting body mass index (BMI), blood pressure, glucose homeostasis, and waist circumference [114]. Moreover, the *Bifidobacterium adolescentis* IVS-1, the *Bifidobacterium lactis* BB-12, and the galacto-oligosaccharides showed no synergistic effects in obese patients [115]. Furthermore, a meta-analysis showed that the supplementation of synbiotics revealed no significant effects on body weight and body fat [116].

The improvement of obese patients is often accompanied by the regulation of gut microbial metabolites [117]. The intake of *Bifidobacterium lactis* UBBLa-70 and fructooligosaccharide for 8 weeks could increase bacterial-related metabolites like pyruvate and alanine in circulation in 32 obese women, while decrease the levels of citrate and branched-chain amino acids [118]. Further evidence implied that butyric acid possessed the potential capability to be a supportive agent in the prevention of obesity due to the properties of regulating circulation and nervous systems, as well as improving intestinal barrier, carbohydrate metabolism, immunomodulation, and appetite control [119].

In short, the *Lactobacillus* and *Bifidobacterium* strains are the most concerning probiotics and the combination of multiple probiotics possess better applied prospect. Moreover, the *Prevotella*-rich enterotype people are more sensitive to probiotics treatment than the *Bacteroides*-rich enterotype. However, the synergistic effects of probiotics and prebiotics, as well as the exact biological effects of postbiotics remain uncertain. So, the optimized formulas of synbiotics and more clinical trials for postbiotics are still needed (Table 2).

| Supplements | Doses | Duration | Sample Size | Target Disease | Main Effects | Ref. |
|-------------|-------|----------|-------------|----------------|-------------|------|
| Probiotics  |       |          |             |                |             |      |
| *Bifidobacterium animalis* SGB06, *Bifidobacterium bifidum* SGB02, *Lactobacillus acidophilus* SGL11, *Lactobacillus delbrueckii* DSM 20081, *Lactococcus lactis* SGL01, *Lactobacillus plantarum* SGL07, *Lactobacillus reuteri* SGL01, *Streptococcus thermophilus*, and *Streptococcus thermophilus* | 1.5 × 10⁹ CFU | 3 weeks | 60 | Obesity | Improving body composition, bacterial composition, and psychopathological status. | [100] |
| *Bifidobacterium lactis* B15 | 2.72 × 10⁹ CFU | 45 days | 45 | Obesity | Improving obesity, blood lipids, and inflammatory markers such as TNF-α and IL-6. | [99] |
| *Bifidobacterium breve* CBT BR3 and *Lactobacillus plantarum* CBT LP3 | 15 × 10⁹ CFU | 12 weeks | 50 | Obesity | More effectively improve obesity biomarkers in patients with *Prevotella*-rich enterotype than *Bacteroides*-rich enterotype. | [102] |
| *Bifidobacterium lactis* BB-12 and *Lactobacillus acidophilus* La-5 | 10⁸ CFU | 6 weeks | 50 | Type 2 diabetes mellitus | Improving fructosamine, HbA1c and IL-10 levels. | [120] |
| *Lactobacillus reuteri* strain ADR-1 and ADR-3 | 4 × 10⁹ CFU for ADR-1, 2 × 10⁸ CFU for ADR-3 | 12 weeks | 68 | Type 2 diabetes mellitus | Decreasing HbA1c and cholesterol levels. | [121] |
| Fermented milk processed by *Lactobacillus casei* strain Shirotta | 80 mL | 16 weeks | 70 | Type 2 diabetes mellitus | Increasing Clostridium coccoidei, Clostridium leptum, and Lactobacillus. Decreasing of translocated gut bacteria. | [122] |
Table 2. Cont.

| Supplements | Doses | Duration | Sample Size | Target Disease | Main Effects | Ref. |
|-------------|-------|----------|-------------|----------------|--------------|-----|
| Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, and Bifidobacterium bifidum | 6 × 10⁹ CFU | 14–16 weeks' gestation | 423 | Gestational diabetes mellitus | Decreasing the relapse prevalence of diabetes mellitus. Not preventing gestational diabetes mellitus. Not affecting weight gain. Not improving depression, anxiety, and physical well-being status. | [123] |
| Bifidobacterium bifidum, Lactobacillus casei, and Lactobacillus acidophilus | 1 × 10⁹ CFU | 16–28 weeks' gestation | 411 | Gestational diabetes mellitus | Improving glucose metabolism. Not affecting weight gain. Not improving depression, anxiety, and physical well-being status. | [124] |
| Bifidobacterium bifidum, Lactobacillus casei, and Lactobacillus acidophilus | 1 × 10⁸ CFU | 24–28 weeks' gestation | 28 | Gestational diabetes mellitus | Improving glucose metabolism. Not affecting weight gain. Not improving depression, anxiety, and physical well-being status. | [125] |
| Bifidobacterium bifidum and Lactobacillus casei | 6.5 × 10⁶ CFU | 17–36 weeks' gestation | 230 | Gestational diabetes mellitus | Improving cognitive function and metabolic status. | [126] |
| Bifidobacterium bifidum and Lactobacillus casei | 2 × 10⁶ CFU/g | 12 weeks | 60 | Type 2 diabetes mellitus | Improving insulin resistance, C-reactive protein, and total glutathione level. | [127] |
| Bifidobacterium bifidum, Lactobacillus casei, and Lactobacillus acidophilus | 2 × 10⁶ CFU/g | 8 weeks | 40 | Major depressive with metabolic disorder | Improving the grade of fatty liver and the serum levels of aminotransferase enzymes. | [128] |
| Yacon | 25 g | 6 weeks | 26–40 | Obesity | Increasing the plasma antioxidant capacity. Decreasing oxidative stress and focal SCFAs levels. Decreasing energy intake by modifying appetite. Improving metabolic endotoxemia. Decreasing PAI1 level. Regulating appetite. Increase Bifidobacterium. Improving glycemic status, lipid profiles, and immune markers. Enhancing beneficial effects of calorie-restricted diet on fat mass and TC level. Improving the grade of fatty liver and the serum levels of aminotransferase enzymes. | [106,107] |
| Inulin oligofructose | 8 g/day | 16 weeks | 42 | Obesity | Improving body fat gain. | [108] |
| Oligofructose | 21 g | 12 weeks | 37 | Obesity | Improving body fat gain. | [109] |
| Inulin-type fructan and whey protein | 5–8 g | 12 weeks | 125 | Obesity | Improving body fat gain. | [110] |
| Inulin oligofructose | 10 g/day | 2 months | 46 | Type 2 diabetes mellitus | Improving the grade of fatty liver and the serum levels of aminotransferase enzymes. | [111] |
| Inulin | 10 g/day | 8 weeks | 45 | Obesity-related major depressive | Improving the grade of fatty liver and the serum levels of aminotransferase enzymes. | [112] |
| Inulin | 10 g/day | 3 months | 75 | NAFLD | Improving body fat gain. | [113] |
| Symbiotics | Growing up milk, Bifidobacterium breve, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus casei, Streptococcus thermophiles, plus fructo-oligosaccharides | 10⁵ CFU/g and 35 mg | 8 weeks | 76 | Obesity | Improving serum insulin level and insulin resistance | [114] |
| Bifidobacterium bifidum, Lactobacillus casei, and Lactobacillus acidophilus | 2 × 10⁹ CFU/g and 0.8 g | 8 weeks | 59 | Obesity | Improving lipid profiles and psychological status. Not benefiting BMI, blood pressure, glucose metabolism, and waist circumference. Improving intestinal barrier function as single agents. No synergistic effects. | [115] |
| Bifidobacterium adolescentis PB-1, Bifidobacterium lactis BB-12, plus galacto-oligosaccharides | 1 × 10⁹ CFU and 5 g | 3 weeks | 114 | Obesity | Improving lipid profiles and psychological status. Not benefiting BMI, blood pressure, glucose metabolism, and waist circumference. Improving intestinal barrier function as single agents. No synergistic effects. | [116] |
| Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus casei W56, Lactobacillus brevis W63, Lactobacillus salivarius W24, Lactococcus lactis W58, and Lactococcus lactis W59, plus galacto-oligosaccharides P11 and fructo-oligosaccharides P6 | 100 mL and 25 g | 12 weeks | 60 | Type 2 diabetes mellitus | Improving body fat gain. | [117] |
| Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus casei, and Lactobacillus acidophilus | 1.5 × 10⁹ CFU and 9 g | 6 months | 26 | Type 2 diabetes mellitus | Improving body fat gain. | [118] |
Table 2. Cont.

| Supplements | Doses | Duration | Sample Size | Target Disease | Main Effects | Ref. |
|-------------|-------|----------|-------------|----------------|--------------|-----|
| Bifidobacterium, Lactobacillus, and Streptococcus thermophilus plus fructo-oligosaccharide | 500 mg/day | 9 weeks | 70 | Type 2 diabetes mellitus, Prediabetes mellitus | Improving HbA1c, BMI, and microalbuminuria. Not restoring the balance of gut microbiota. | [135] |
| Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, and Lactobacillus acidophilus plus inulin | $1.5 \times 10^{9}$ CFU and 6 g | 6 months | 120 | Prediabetes mellitus | Not restoring the balance of gut microbiota. | [136] |
| Bifidobacterium lactis plus fructo-oligosaccharides | $5 \times 10^{9}$ CFU/bag and 4.95 g/bag | 30 days | 27 | Digestive disorder | Improving intestinal function. Decreasing IL-6, IL-8, IL-17α, and IFN-γ levels. | [137] |
| Bifidobacterium lactis, Lactobacillus acidophilus, and Lactobacillus casei plus chicory inulin | $7 \times 10^{9}$ CFU and 100 mg | 4 months | 28 | NAFLD | Improving fatty liver grade, and inflammatory and antioxidative status. | [138] |
| Bifidobacterium bifidum, Bifidobacterium longum, and Lactobacillus acidophilus plus selenium Postbiotics | $2 \times 10^{9}$ CFU and 200 mg | 12 weeks | 79 | Alzheimer’s disease with metabolic disorder | Improving the cognitive function and metabolic function. | [139] |
| Hydroxyl-methyl butyrate | 3 g | 1 week | 34 | Diabetic-related sarcopenia | Inhibiting catabolic effect on skeletal muscle. Improving alimentary canal function. | [140] |
| Butyrate | 80 mM | 3 days | 80 | Bacillary dysentery with metabolic disorder | Alleviating pathological impairment of colonic mucosa barrier Enhancing antimicrobial peptides release. | [141] |

Abbreviation: BMI, body mass index; HbA1c, hemoglobin A1c; IL-6/8/10/17α, interleukin-6/8/10/17α; IFN-γ, interferon-γ; PAI1, plasminogen activator inhibitor 1; SCFAs, short-chain fatty acids; TC, total cholesterol; TNF-α, tumor necrosis factor α.

4.2. Type 2 and Gestational Diabetes Mellitus

A clinical trial with 50 patients with type 2 diabetes mellitus showed that the daily intake of 120 g fermented milk containing Bifidobacterium lactis BB-12 and Lactobacillus acidophilus La-5 ($10^{9}$ CFU for each) for 6 weeks improved serum levels of fructosamine, hemoglobin A1c (HbA1c), and IL-10 [120]. Moreover, both Lactobacillus reuteri ADR-1 and ADR-3 strain could decrease the levels of serum HbA1c and cholesterol with regulating Bacteroidetes and Bifidobacterium abundances in 68 patients with type 2 diabetes mellitus, and the ADR-3 strain revealed a better effect on decreasing blood pressure and Firmicutes abundance than the ADR-1 strain [121]. Moreover, the intake of fermented milk processed by Lactobacillus casei Shirota for 16 weeks restricted the translocation of gut bacteria into blood circulation in 70 patients with type 2 diabetes mellitus, leading to the increased abundances of Clostridium cocoides, Clostridium leptum, and Lactobacillus in fecal [122]. Furthermore, several meta-analyses showed the benefits of probiotics treatment on improving HbA1c and fasting insulin [142,143].

The effects of probiotics on gestational diabetes mellitus remained controversial [144]. The clinical trials on pregnant women with normal body weight reported that the daily supplementation of Lactobacillus rhamnosus HN001 ($6 \times 10^{9}$ CFU) could lower the risk and relapse prevalence of diabetes mellitus, whereas the probiotics containing Bifidobacterium lactis and Lactobacillus rhamnosus did not prevent gestational diabetes mellitus in pregnant women with overweight or obesity [123,124]. Further evidence from 230 pregnant women with obesity revealed that the daily intake of probiotics containing Bifidobacterium lactis BB12 and Lactobacillus rhamnosus GG ($6.5 \times 10^{9}$ CFU for each) for 36 weeks did not improve depression, anxiety, and physical well-being status during pregnancy [126]. So, the bodyweight condition might be the critical factor for the effects of probiotics on gestational diabetes mellitus [125].

Prebiotics also exerted a potential in the prevention of type 2 diabetes mellitus by modulating gut microbiota dysbiosis [145,146]. A randomized placebo-controlled trial on 46 patients with type 2 diabetes mellitus showed that the intake of 10 g/day oligofructose-enriched inulin for 2 months improved glycemic status, lipid profiles, and immune biomarkers [129]. Besides, the effects of synbiotic supplementation on patients with type 2 diabetes
mellitus attracted more and more attention, and the Coix lacryma-jobi could enhance the effect of probiotic yogurt in reducing body weight and fasting blood glucose [133]. Besides, another clinical trial indicated that synbiotics intervention just revealed a limited benefit in diabetic-related biomarkers without improving glucose metabolism [134]. Moreover, a 9-week intake of 500 mg/day synbiotics containing Bifidobacterium, Lactobacillus, Streptococcus thermophilus, and fructo-oligosaccharide only improved the HbA1c, BMI, and microalbuminuria in 70 patients with type 2 diabetes mellitus, without changing fasting blood glucose, lipid profiles, and creatinine [135]. Furthermore, a clinical trial compared the effects between probiotics (Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, and Lactobacillus acidophilus, 1.5 × 10⁹ CFU for each) and synbiotics (the probiotics plus inulin) on 120 prediabetic adults, turned out that a 6-month intake of synbiotics failed to regulate gut microbial composition [136].

In general, probiotics alleviated type 2 diabetes mellitus, but the clinical application of probiotics in gestational diabetes mellitus with obesity needs further investigation. Besides, the application of bacterial-processed prebiotics is an emerging trend in clinical exploration, and the optimal formula of synbiotics as well as the specific efficacy of postbiotics on diabetes mellitus still needs more tests.

4.3. Other Metabolic Diseases

Metabolic impairment is a common complication of nervous system dysfunction like Alzheimer’s disease and depression [147,148]. A clinical trial on 60 patients with Alzheimer’s disease showed that a 12-week intake of probiotic milk containing Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus casei, and Lactobacillus fermentum at a dose of 200 mL/day (2 × 10⁹ CFU/g for each) improved cognitive function and metabolic status [127]. Likely, an 8-week consumption of probiotics (Bifidobacterium bifidum, Lactobacillus acidophilus, and Lactobacillus casei, 2 × 10⁹ CFU/g for each) improved metabolic status with 40 patients with major depressive disorders [128].

Prebiotics could also benefit obesity-related major depressive disorder, and the patient who received an additional 10 g/day of inulin showed a better improvement in fat mass and TC level compared to the patient who received a calorie-restricted diet alone [130]. Besides, a double-blind, placebo-control clinical trial with 75 NAFLD patients showed that the consumption of prebiotic inulin at doses of 10 g/day for 3 months could improve the grade of fatty liver and the serum levels of aminotransferase enzymes [131].

Synbiotics supplement is a promising way for controlling the prevalence of NAFLD and nervous system impairment. For example, the Bifidobacterium strains were widely used in different formulas of synbiotics, and the daily intake of synbiotics containing Bifidobacterium lactis, Lactobacillus acidophilus, and Lactobacillus casei (7 × 10⁹ CFU for each) and chicory inulin (100 mg) for 4 months could improve fatty liver grade, inflammatory and antioxidative status in 28 children with obesity-related NAFLD [138]. Moreover, a clinical trial on 79 patients with Alzheimer’s disease revealed that the daily consumption of selenium (200 mg) accompanied with Bifidobacterium bifidum, Bifidobacterium longum, and Lactobacillus acidophilus (2 × 10⁹ CFU for each) for 12 weeks could more effectively improve the cognitive function and metabolic function than the single selenium treatment [139]. Furthermore, the combination of Bifidobacterium lactis (5 × 10⁹ CFU/bag) and fructo-oligosaccharides (4.95 g/bag) could improve gastrointestinal discomfort, with decreasing the plasma levels of IL-6, IL-8, IL-17α, and interferon-γ (IFN-γ) [137]. Besides, a meta-analysis showed that the co-treatment of probiotic strains (like Bifidobacterium and Lactobacillus) and prebiotic food (like cheese) revealed the potential to be an effective intervention for metabolic syndrome [149].

Patients with inflammatory bowel disease were often accompanied with metabolic disorders and the depletion of butyrate-producing bacteria, and the oral intake of butyrate could enhance the efficacy of regular therapy with decreasing the Bacteroides fragilis to Faecalibacterium prausnitzii ratio [150]. Moreover, hypertension was a common complication of type 2 diabetes mellitus, and the patients who received antihypertensive medications
over 3 months showed an increase in butyrate level and a decrease in acetate level, with 
reducing the levels of circulating fibroblast growth factor 21 (FGF 21), tumor necrosis 
factor superfamily member 14 (TNFSF 14) and TNF-α [151]. Furthermore, sarcopenia is 
a complication of the elderly diabetic population, and the utilization of butyrate-related 
derivatives like hydroxyl-methyl butyrate revealed a promising potential in mitigating 
sarcopenia [140]. In addition, bacillary dysentery is caused by the infection of Shigella 
germ, which leads to the destruction of the colonic mucosa barrier and metabolic disorders, 
and the adjunct therapy with butyrate could correct colonic impairment and promote 
antimicrobial peptides release [141].

In summary, PPSP reveal beneficial effects on metabolic-related diseases like nervous 
system dysfunction, hypertension, and NAFLD, meanwhile, most of the synbiotics formu-
las are based on Bifidobacterium and Lactobacillus. Besides, butyrate and related derivates 
are the most focused postbiotics but still need more clinical assessment.

5. Conclusions

Metabolic diseases are closely associated with gut microbiota dysbiosis. PPSP possess 
beneficial effects on controlling metabolic diseases such as obesity and type 2 diabetes 
mellitus by targeting gut microbiota. Since the beneficial effects of PPSP on alleviating 
metabolic diseases, researchers keep exploiting different compatible solutions for the best 
therapeutic effect and turns out that the co-intervention of multiple alive bacteria strains 
could be a promising way. Also, novel food processing strategies like enzyme-modified 
prebiotics and probiotic-fermented natural foods have been developed to enhance the ben-
eficial effects. Moreover, the in vitro and in vivo studies reveal that the modulation of gut 
microbiota composition is one of the most direct mechanisms of PPSP to alleviate metabolic 
disease, manifesting as regulating the abundances of Akkermansia, Bacteroidetes, Blautia, Bifi-
dobacteria, Bifidobacterium, Collinsella, Clostridiaceae, Christensenellaceae, Desulfovibrionaceae, 
Firmicutes, Lachnospiraceae, Lactobacillus, Proteobacteria, Rikenellaceae, Ruminococcaceae, and 
Yersinia. Furthermore, PPSP also indirectly ameliorate metabolic diseases by regulating 
gut microbial metabolites, such as acetate, propionate, butyrate, isovalerate, lactic acid, 
and palmitoylthanolamide, while suppressing the production of LPS and TMAO, as well 
as reducing the bile acid pools. Additionally, the improvement of the intestinal barrier 
function plays an important role in attenuating metabolic diseases, with upregulating 
claudin 1, GLP1, IL-10, occludin 1, and ZO-1 expressions. These mechanisms collectively 
 improve the whole metabolic system by targeting several pivotal signaling pathways, such 
as upregulating Akt, AMPK, CPR1α, ERK, GPR43, NLCR3, NOD2, GLUT2/4, IRF4, p38 
MAPK, PPARx, SIRT1, TLR2, and TRAF6-mediated pathways, while downregulating ACE, 
NF-κB, NOD1, TLR4, and TNF-α-related pathways. Furthermore, several clinical trials 
have showed the effects of PPSP on metabolic diseases, and more researches are needed on 
the situation when patients are during pregnancy. In addition, the optimized formula of 
synbiotics and the specific efficacy of postbiotics on humans are worthy of further explo-
ration. Besides, the recent researches are mostly focusing on the effects and mechanisms of 
PPSP on obesity and type 2 diabetes mellitus. In the future, more attention should be paid 
to other metabolic diseases, such as cardiovascular diseases and hyperuricemia.

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