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Review

The Role of Gut Microbiota Modulation Strategies in Obesity: The Applications and Mechanisms

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Abstract: Nowadays, obesity is a leading public health problem worldwide. The growing prevalence of obesity significantly accounts for other cardio-metabolic diseases, including hypertension and diabetes. Several studies have shown that obesity is strongly associated with genetic, environmental, lifestyle, and dietary factors, especially the disordered profiles of gut microbiota (GM). The present review concluded mechanistic studies and potential correspondent treatments for obesity. Specifically, the anti-obesity effects of food-derived compounds manipulating GM were highlighted. The potential limitations of bioactive compounds on absorption in the intestinal tract were also discussed. Thus, the future direction of fecal microbiota transplantation (FMT) as an approach to support modulating host GM (considered to be a potential therapeutic target for obesity) was discussed. This review shed light on the role of GM modulation strategies for the prevention/treatment of obesity.

Keywords: obese; intestinal flora; mechanism; bioactive food; dysbiosis

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1. Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation. Usually, body mass index (BMI) is used to classify these conditions (overweight $\geq$25 kg/m^2; obesity $\geq$30 kg/m^2). Until recently, higher BMI was strongly associated with the incidence of several adverse comorbidities (cardiovascular disease and type 2 diabetes), becoming one of the most significant and fastest-growing public health problems in developed and developing countries [1]. The segment of the population with a BMI of 25 kg/m^2 or more grew worldwide between 1980 and 2019 (28.8% to 36.9% in men and 29.8% to 38.0% in women: Figure 1a). Over the past 20 years, the prescription of anti-obesity medications has remained less efficient compared to pharmacotherapy for other metabolic illnesses (e.g., hypertension). On the other hand, all anti-obesity medicines are contraindicated for use in pregnant women and adolescents [2]. The prevalence of obesity has necessitated increased efforts toward the development of natural remedies and dietary interventions, which could be safer alternatives to synthetic drugs for managing the disease.

Genetic factors, dietary habits, sedentary lifestyle, and, especially, gut microbiota (GM) correlating to host signaling pathways, play a crucial role in human metabolic disease. Based on the above situation, a growing body of evidence indicates that anti-obesity food-derived phytochemicals can be classified into four categories based on their distinct mechanisms (the entire obesity mechanistic studies are listed in Figure 2), including improved GM, decreased lipid absorption through inhibition of digestive enzyme activity, decreased pre-adipocyte differentiation and proliferation, and increased lipolysis [3]. Additionally, fecal microbiota transplantation (FMT) is a cutting-edge strategy for manipulating the entire GM (from dysbiosis to eubiosis), based on the idea of the microbiome as a potent agent in obesity. Figure 1b depicts the growing interest in obesity and GM during the last decade.

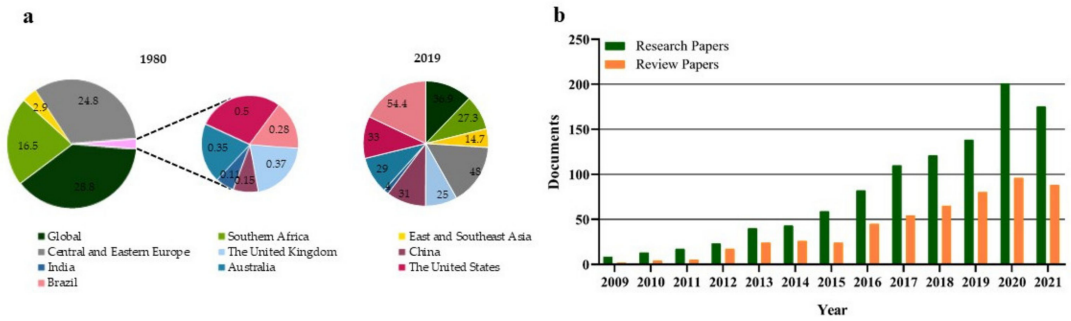

Figure 1. (**a**) The prevalence of overweight and obese adults increased in 1980 and 2019 in different regions and countries worldwide. The data come from Global Burden of Disease (GBD), a research program on the burden of disease that evaluates mortality and disability due to major disease, injury, and risk factors. (**b**) A number of articles were published on the anti-obesity effects of food products affecting gut microbiota over the period 2009–2021, according to the Web of Science Database (last accessed 25 December 2021, documents search: "food AND obesity AND gut microbiota").

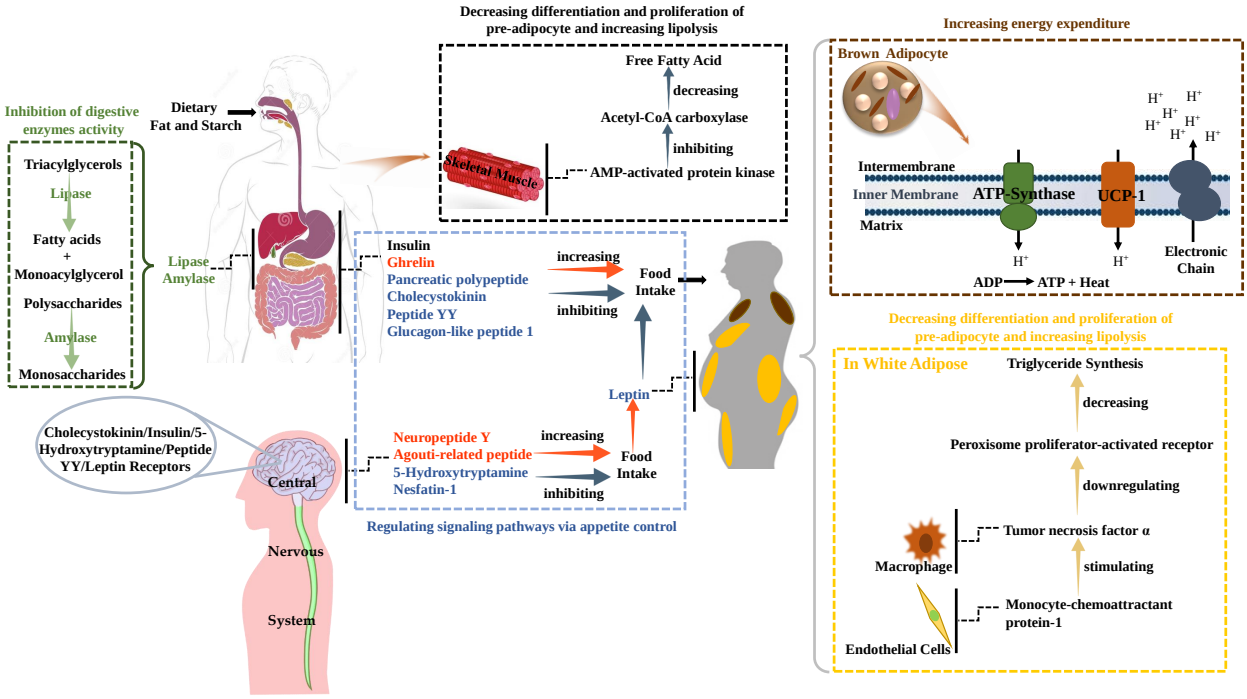

Figure 2. The etiology of obesity and potential corresponding treatment for obesity. Interactions between diet, digestive enzyme, energy intake, modulation of appetite, and the differentiation and proliferation of pre-adipocyte are shown. The orange words represent orexigenic mediators and blue words represent anorexigenic mediators.

Thus, this work aimed to provide an overview on the etiology (particular GM) of obesity according to a wealth of research. Moreover, we aspired to present the latest findings of anti-obesity dietary modification relating to host GM. Then, FMT was also emphasized in this review, which could help in unraveling the complex interaction between obesity and GM.

2. Gut Microbiota Dysbiosis in Obesity

Imbalanced gut microbiota are associated with obesity. Figure 3 depicts the alteration of the intestine's homeostatic balance, resulting in the changing of downstream metabolites in obese. For example, bile acids (BAs) are the essential regulator of lipid metabolism, promoting nutrient and vitamin absorption and transport. In the small intestine, primary

BAs are converted into secondary form by bacterial deconjugation and dihydroxylation [4]. Furthermore, ingestible polysaccharides are used as growth substrates of GM to produce short-chain fatty acids (SCFAs) [3]. SCFAs attach to receptors on entero-endocrine cells, and affect the release of enteric hormones into the bloodstream, further allowing glucose, ghrelin production, and obesity to develop [5]. Notably, SCFAs can bind to the G-protein-coupled receptors (GPCRs) GPR41 and GPR43, thereby triggering glucagon-like peptide 1 (GLP-1) secretion by the L-cells [3]. SCFA might also indirectly affect muscle insulin sensitivity via increased systemic levels of gut-derived GLP-1 further, thereby affecting skeletal muscle insulin action and contributing to improved muscle insulin sensitivity [4]. Additionally, glutamate, an amino acid, can be converted to gamma-aminobutyric acid (GABA) by certain lactic acid bacteria, which then expresses GABA-binding proteins and 5-hydroxytryptamine (5-HT) to control appetite [6]. Moreover, it is well known that obesity has long been associated with chronic inflammation and insulin resistance, both of which may be triggered by lipopolysaccharide (LPS) [3]. LPS is the principal component of the outer membrane of Gram-negative bacteria. Recent studies have elucidated that higher concentrations of LPS are released as the result of bacterial death when the gut stable environment is broken, and it can enter serum due to leakage of the intestinal wall induced by tight junction protein dysfunction, thus causing inflammatory response. In conclusion, GM is an important part of overcoming obesity.

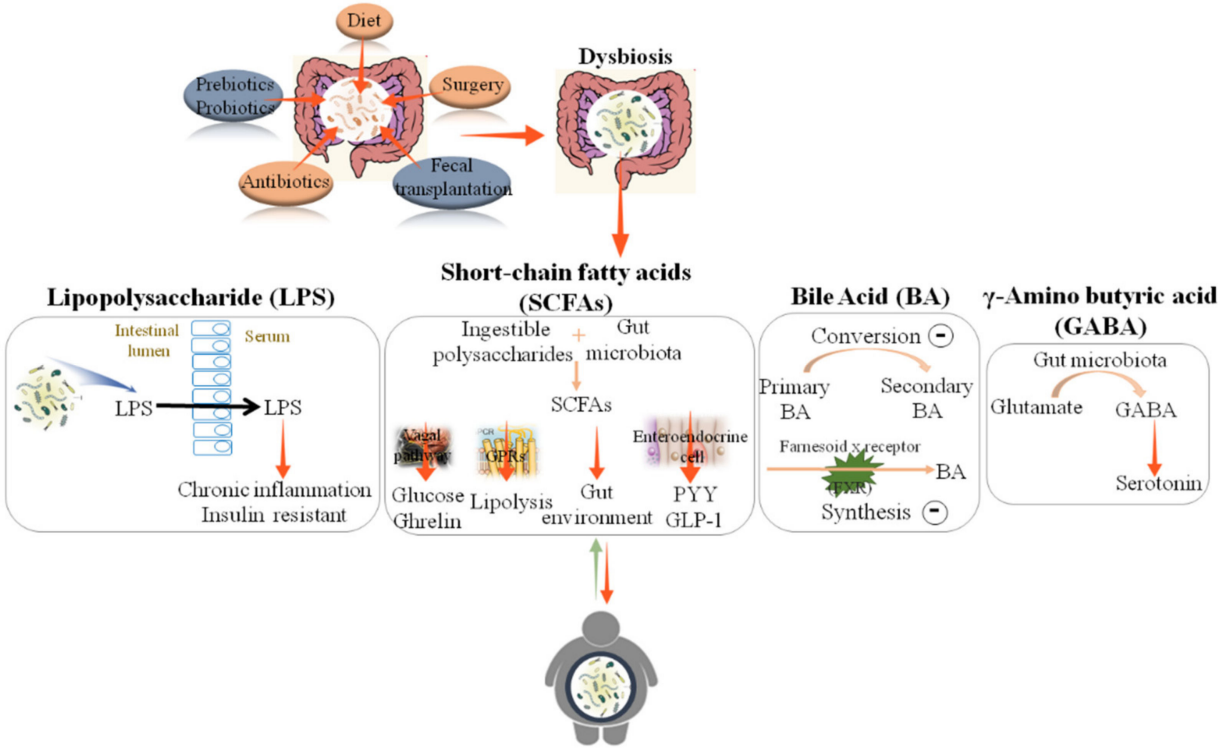

Figure 3. Interaction of altered gut microbiota and downstream metabolic effects influencing obesity.

3. The Mechanistic Studies on Obesity and Related Treatment Methods

3.1. Inhibition of Digestive Enzymes Activity

As shown in Figure 2, lipase, a pancreatic enzyme, hydrolyzes dietary triacylglycerols into monoacylglycerol and free fatty acids (FFA), which are digested by enterocytes, and resynthesized into triacylglycerols stored in adipocytes. When lipid breakdown is prevented by a pancreatic lipase inhibitor, the utilization of ingested lipids is reduced. Other enzymes, e.g., amylase, used to break down starch (the largest source of calories), can convert polysaccharides to monosaccharides. As a result, amylase inhibitors can be helpful in impeding carbohydrate absorption [7].

3.2. Regulating Signaling Pathways via Appetite Control

Obesity is caused by a mismatch between energy intake and expenditure. Many signaling molecules in the central nervous system (CNS) can help in the regulation of appetite (Figure 2). For example, Neuropeptide Y (NPY), agouti-related peptide (AgRP), and ghrelin are some of the orexigenic signaling molecules. Fasting upregulates NPY and AgRP expression, while the suppression in adipose tissues generates leptin [8]. As a result, ghrelin antagonism may reduce or increase appetite, making it a possible supplementary treatment for obesity. Other molecules, like nesfatin-1, 5-HT, and cholecystokinin (CCK), which act as the anorexigenic mediators that reduce food intake, are deeply related to body weight. Moreover, in the stomach, peptide YY (PYY1-36) and PYY3–36 are two endogenous circulating versions produced in the stomach [9]. In the pancreatic islets, the anorectic effects of pancreatic polypeptide (PP), which are generated by PP cells in response to a meal, are thought to be mediated directly through the brainstem and hypothalamus Y4 receptors [10]. Thus, one effective method of weight loss is to regulate anorexigenic mediators.

Gut hormones, as illustrated in Figure 2, including PYY, GLP-1, PP, and ghrelin, regulate food consumption in the short term, while insulin and leptin regulate long-term energy balance [11]. Insulin and leptin levels in the blood are positively correlated with adipose tissue mass; within the CNS, insulin works as an anorectic signal [12]. Leptin (also as an anorectic signal) is primarily released by adipocytes, with circulating levels proportional to fat content. It exerts its anorectic action via the arcuate nucleus of the hypothalamus (ARC) [13]. Leptin reduces food intake by inhibiting NPY/AgRP neurons and activating pro-opiomelanocortin/cocaine-and amphetamine-regulated transcript (POMC/CART) neurons in ARC [14].

3.3. Increasing Energy Expenditure

As shown in Figure 2, in various anatomical locations of humans, brown adipose tissues (BAT) are distributed from the neck to the clavicle [15]. Uncoupling protein-1 (UCP-1) is a mitochondrial BAT-specific protein that catalyzes protons through the inner mitochondrial membrane by discharging the proton gradient created in oxidative phosphorylation and releases energy in the form of heat [16]. Thus, looking for drugs that boost UCP1 gene expression could be a good way to reduce obesity by increasing energy expenditure [16].

3.4. Decreasing Differentiation and Proliferation of Pre-Adipocyte and Increasing Lipolysis

Adipocytes in white adipose tissue (WAT) are vital in regulating lipid homeostasis and energy balance [17]. Hypertrophy of WAT adipocytes is closely linked to adipose dysfunction, and hyperplasia suggests increased adipogenesis [18]. As a result, natural compounds that directly target adipogenesis inhibition were thought to be promising in terms of their potential in treating obesity. Additionally, obesity is associated with low-level chronic inflammation, exacerbated by macrophage infiltration in WAT [19]. Endothelial cells release monocyte-chemoattractant protein-1 (MCP-1), which stimulates macrophage infiltration and the generation of the inflammatory mediator tumor necrosis factor (TNF-α) (Figure 2) [20]. Inflammatory cytokines decrease triglyceride formation by downregulating peroxisome proliferator-activated receptor (PPAR) [21].

Pharmaceutically-targeted lipolysis can be achieved by modulating free fatty acid (FFA) synthesis. In the molecular pathways, Figure 2 illustrates that AMP-activated protein kinase (AMPK) activation promotes glucose transport in skeletal muscles, decreasing FFA production via inhibiting the action of acetyl-CoA carboxylase (ACC) [22]. Additionally, specific genetic programs for the transport and storage of FFA can be triggered in non-adipose tissues in response to dietary overload, resulting in ectopic fat deposition [17]. Thus, in the aspect of lipolysis, reducing FFA synthesis could be helpful for obese.

4. Food-Derived Compounds in GM Modulation and Their Anti-Obesity Effects

The imbalance of GM (dysbiosis) is related to metabolic disorders. According to previous research, the bloom of pathobionts (the members of the commensal microbiota

that have the potential to cause pathology), loss of commensals, and loss of diversity are three types of dysbiosis. Generally, the majority of the GM is composed of strict anaerobes, which dominate the facultative anaerobes and aerobes by 2–3 orders of magnitude. In the human body, GM is dominated by 2 of them, the *Bacteroidetes* and the *Firmicutes*, whereas *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* are present in minor proportions [5]. In recent years, there have been more studies about the impact of intestinal microorganisms on obese individuals. Some studies found little association between BMI and changes in GM composition at the phylum level, while differences were observed to occur at the genus/species level between the obese and healthy state. However, some studies reported much lower *Bacteroidetes* in obese individuals and proposed that a high *Firmicutes* to *Bacteroidetes* ratio was characteristic of the obese state. This was followed by research focused on the anti-obesity effects of functional food compounds based on modulating GM. Tables 1–4 summarize the studies of various food materials during in vivo and in vitro analysis for obesity. We attempted to figure out the potential anti-obesity impact of different functional compounds for the intervention of intestinal microorganisms in obese individuals.

4.1. Anti-Obesity Effect of Different Food Extracts and Gut Modulation

The extraction process is one of the simplest methods to extract various bioactive compounds with anti-obesity properties from raw food. It provides an easy way to screen the impact of functional ingredients on the GM modulation in animal models. As shown in Table 1, food extract has anti-obesity properties through GM regulation and metabolism [23–26].

Table 1. Bioactive extract of food against obesity in vitro/in vivo, based on gut microbiota.

Food	Experimental Results		Reference
	In Vivo/In Vitro	**Gut Microbiota**	
Jamun	Alleviated insulin resistance, liver steatosis	Restored the *Firmicutes*/*Bacteroidetes* and SCFAs	[23]
Codium fragile	Decreased the size of adipocytes, levels of cholesterol and glucose	Increased the *Bacteroidetes*; decreased the *Verrucomicrobia*	[24]
Citrus peel	Decreased lipid content, adipocyte size, adipose tissue weight	Increased *Prevotella*; decreased *rc4-4* bacteria	[25]
Aged citrus peel	Reduced the mass of adipose tissues, adipocyte size	Increased fecal SCFAs; decreased *Proteobacteria*, *Firmicutes*/*Bacteroidetes*	[27]
Blueberry	Returned lipid metabolism to normal	Modulated *Proteobacteria*, *Deferribacteres*, *Actinobacteria*, *Bifidobacterium*	[28]
Caffeic acid	Reduced fat accumulation; improved lipid profile	Increased the anti-obesity related and butyrate-producing bacteria	[29]
–	Prevented perirenal, epididymal fat accumulation; decreased serum total cholesterol (TC), leptin and triglycerides (TG)	Decreased *Firmicutes*; increased *Bifidobacterium*, fecal acetic acid, propionic acid, total SCFAs	[30]
Rosadavurica Pall.	Inhibited the liver, kidney, epididymal adipose tissue weight	Decreased the *Erysipelotrichaceae*.	[26]
Green and Black tea	Decreased subcutaneous, epididymal fat	Decreased *Firmicutes*; increased *Bacteroidetes*, *Pseudobutyrivibrio*	[31]
–	Reduced lipid levels in plasma	Inhibited *Desulfovibrionaceae*, *Ruminococcaceae*; raised the *Bacteroidaceae*, *Lactobacillaceae*	[32]
Capsaicin (CAP)	Lowered triglyceride, cholesterol, glucose, and insulin levels	Increased the *Akkermansia*, *Bacteroides*; reduced the *Desulfovibrio*, *Escherichia*, *Helicobacter*,	[33]

Table 1. *Cont.*

Food	Experimental Results		Reference
	In Vivo/In Vitro	**Gut Microbiota**	
Capsicumannuum L.	Reduced the serum TG, TC, low density lipoprotein (LDL-C) levels; reversed glucose tolerance	Increased the *Bifidobacterium* and *Akkermansia*; decreased the *Ruminococcus* and *Firmicute/Bacteroidetes*	[34]
C.pyrenoidosa S.platensis	Protected, dyslipidemia, fat deposition; increased lipolysis and decreased lipogenesis	Increased *Clostridia*, *Bacterioidia*; decreased *Actinobacteria*, *Verrucomicrobia*; restored the SCFAs, BA	[35]
L.barbarum	Decreased serum TC, TG, and LDL-C	Improved community diversity of intestinal flora; could increase the content of SCFAs	[36]
Polymannuronic acid	Reduced the blood triacylglycerol levels and improved glucose tolerance	Increased the abundance of probiotic bacteria like *Lactobacillus reuteri*	[37]
Chitosan	Increased the serum leptin level, oral glucose tolerance	Increased *Coprobacillus cateniformis*; decreased *Clostridium lactatifermentans*	[38]
–	Improved glucose intolerance	Increased the *Bifidobacterium*, *Lachnospiraceae_NK4A136_group* and *Roseburia*	[39]

4.1.1. Polyphenolic Compounds

Polyphenolic compounds, after consumption, may undergo absorption and phase II reactions in the small intestine. The majority of the undigested fraction is sent to the colon to interact with GM bidirectionally [40]. As listed in Table 1, blueberry polyphenols and caffeic acid act as potential prebiotic agents by influencing GM [28,29]. The flavonoids and flavanol monomers known as catechins are the most active components in polyphenolic components, with epigallocatechin-3-gallate and epicatechin-3-gallate being the most effective molecules. In tea, these components showed synergistic anti-obesity benefits by modifying the GM balance [30,31]. Additionally, taxifolin is a natural dihydroflavonol found in many plants and health products. It could help to decrease the ratio of *Firmicutes/Bacteroidetes*, *Proteobacteria* in obese [41]. Additionally, benefits could be obtained from polyphenolic compounds from fruits such as chlorogenic acid, with high antioxidant properties [32,42].

4.1.2. Polysaccharides Compounds

Polysaccharides can act as a substrate for certain beneficial GM in the large intestine, increasing intestinal peristalsis and improving the production of certain metabolites such as SCFAs, resulting in weight loss; for example, *Lycium barbarum* polysaccharides [36,43]. On the other hand, sea-buckthorn polysaccharides were observed boosting p-AMPK α and PPAR α protein expression, as well as reorganizing the GM [44]. Furthermore, microalgae polysaccharides, poly mannuronic acid and chitosan are derived from different food materials; it was proven that they could be used as effective weight-reduction products as a result of improving gut dysbiosis by boosting beneficial bacteria in obese individuals [35,37,38].

4.1.3. Alkaloid and Peptides

Alkaloids are generally harmless, naturally occurring substances that can help prevent or treat metabolic syndrome. In the latest research, *Grifola frondosa* extract, with its abundant alkaloids, lowered the relative abundance of *Romboutsia*, enhancing the quantity of glucose metabolism [45]. Similarly, xylan oligosaccharides changed the composition of GM, increasing the relative population of *Bifidobacterium*, *Lachnospiraceae* NK4A136 group and *Roseburia* [39]. Other alkaloid compounds, like capsaicin, lowered food intake and anti-obesity impact was detected regardless of TRPV1 channel activation, mediated changes in GM populations, and SCFA concentrations [46]. Bioactive peptides, a type of functional food ingredient, have the potential to have a positive impact on human health, in addition to their nutritional value. Food proteins can also release peptides during transit through the gastrointestinal tract, which can have antioxidant and gut modulatory effects on a local

level. Collagen peptides, as a potential anti-obesity agent, were demonstrated to restore gut *Lactobacillus*, *Akkermansia* and *Erysipelatoclostridium* [46].

4.2. Anti-Obesity Effect of Different Food Combinations and Gut Modulations

Most of the research on food bioactive components and GM has focused on the impact of particular food compounds. In processed foods, however, various food ingredients are employed in combination. More research is needed to understand the combined effects of several compounds on GM, which would better reflect real-world situations [47]. Table 2 shows recent research updates on the positive impacts of numerous foods on obesity. For example, when vegetables were consumed alongside Euglena, they were shown to reduce weight by increasing the fraction of SCFA-producing good bacteria [48]. Additionally, consuming cereal, a mixture of millet, maize, oat, soybean, and purple potato could be developed to prevent high-fat diet (HFD)-induced obesity by modulating GM from functional components, such as β-glucan, dietary fiber, resistant starch, and polyphenols in cereals [49]. Mulberry leaf mixture improved the bioaccessibility and bioavailability of two functional components (phenols and fiber), which maximized the anti-obesity effects through the GM-host metabolism pathway [50]. Moreover, the combination of quercetin and resveratrol strengthened the regulation of GM, which was linked to diet-induced obesity [51].

Table 2. Combined different food or compounds against obesity in vitro/in vivo based on gut microbiota.

Food	Experimental Results		Reference
	In Vivo/In Vitro	**Gut Microbiota**	
Euglena gracilis	Reduced visceral fat accumulation and adipocyte area	Increased SCFAs-producing beneficial bacteria; reduced harmful bacteria	[48]
Millet; Maize; Oat; Potato	Decreased fat accumulation; improved the blood glucose tolerance	Promoted the release of SCFAs; increased the *Lactobacillus* and *Bifidobacterium*	[49]
Mulberry leaf	Inhibited adipocyte differentiation and triglyceride synthesis	Reduced *Firmicutes*/*Bacteroidetes* and *Lachnospiraceae*; improved the *Lactobacilli*	[50]
–	Reduced visceral adipose tissue weight, TNF-α, MCP-1, adiponectin, insulin, leptin	Decreased *Desulfovibrionaceae*, *Coriobacteriaceae*; increased *Bacteroidales*, *Christensenellaceae*,	[51]

4.3. Anti-Obesity Effects of Fermented Foods and Gut Modulation

4.3.1. Probiotics

Probiotics are live bacteria that reach the colon in a state of activity sufficient to provide health benefits [52]. Probiotics such as *Lactobacillus plantarum* LB818, *Ligilactobacillus salivarius* LCK11 are good for metabolic disorders, as they modify the gut bacterial community, as illustrated in Table 3 [53,54]. The combination of different probiotics (*L. rhamnosus* 4B15 and *C. tricuspidata*) ameliorated obesity-related metabolic parameters in diet-induced obese mice; combined *L. rhamnosus* LS-8 and *L. crustorum* MN047 showed the same effects [55,56]. Some fermented food-derived probiotics warrant in-depth study, e.g., kimchi [57]. More specifically, *Lactobacillus sakei* ADM14, a probiotic strain found in kimchi, has shown promise in treating metabolic disorders [58].

4.3.2. Fermented Food Materials

Fermented foods are prepared through biotransformation of the original components by controlled microbial fermentation in a food matrix [59]. Microbial fermentation in the food matrix produces lactic acid, alcohol, acetic acid, propionic acid, bioactive peptides, exopolysaccharides, etc. and like compounds [60]. As shown in Table 3, we determined the anti-obesity effects of different fermented foods, including fermented tremella/blueberry, fermented Huyou juice, fermented hazy apple juice, fermented *Monascus ruber* and fermented cereal food [61–65]. Herbal medicines can also benefit from fermentation-driven

bio-activation, boosting their therapeutic potencies and efficacies. According to Choi et al., the fermentation of *Puerariae Radix* increased lactate and enabled the enrichment of particular microbial communities that could aid in the anti-obesity process [66].

Table 3. Fermented food against obesity in vitro/in vivo based on gut microbiota.

Food	Experimental Results		Reference
	In Vivo/In Vitro	Gut Microbiota	
C.tricuspidata	The fat mass, serum triglyceride, and alanine aminotransferase levels were reduced	Modulated *Desulfovibrio*, *Adlercreutzia*, *Allobaculum*, *Coprococcus*, *Helicobacter*, *Flexispira*, *Odoribacter*	[55]
Lactobacillusrhamnosus; *L.crustorum*	Mitigated insulin resistance	Decreased *Bacteroides*, *Desulfovibrio*; increased *Lactobacillus*, *Bifdobacterium* and feces SCFAs	[56]
Lactobacillusplantarum	Decreased deposition of fat droplets; lowered TC, TG	Increased the *Bacteroidetes*, *Akkermansia*, *Lactobacillus*; decreased the *Firmicutes*	[53]
Ligilactobacillus salivariu	Inhibited abdominal, liver fat accumulation, dyslipidemia	Reduced *Firmicutes*/*Bacteroidetes*; shifted overall GM structure	[54]
Kimchi	Decreased adipose tissue; decreased in arachidic acid, stearic acid, fumaric acid, and glucose	*Muribaculaceae* higher, lower *Akkermansiaceae*, *Coriobacteriaceae*, *Erysipelotrichaceae*	[57]
Andong sikhae kimchi	Reduced epididymal fat expansion, total blood cholesterol and glucose levels	Restored the *Firmicutes*/*Bacteroidetes*; increased the *Bacteroides faecichinchillae* and *Alistipes*	[58]
Tremella Blueberry	Dody weight (BW), TG level, fat level and ratio of lipid/BW were lower	*Allobaculum*, *Parabacteroides*, *Prevotella* were increased; pathogenic bacteria were reduced	[61]
Huyou	_	Decreased *Firmicutes/Bacteroidetes*	[62]
Pueraria lobata	Reduced BW gain, adipocyte size	The *S24_7* was increased; enriched *Lactococcus* and *Ruminococcus*	[66]
Panax ginseng Meyer	Decreased serum TC, LDL-C, and lipid accumulation in hepatocytes	Reduced the *Firmicutes*/*Bacteroidetes*, *Muribaculaceae*; increased the *Prevotella_9*	[63]
Black barley	Inhibited liver and abdominal fat indexes; decreased thiobarbituric acid	Increased the *Akkermansia*, *Lactococcus*; Decreased *Firmicutes*/*Bacteroidetes*	[64]
Apples	Inhibited weight gain, fat accumulation; regulated the blood lipid levels	Decreased *Firmicutes*/*Bacteroidotas*; augmented *Akkermansia*, *Bacteroides*	[65]

4.4. Anti-Obesity Effect of Germinated Foods with Gut Modulation

Activated hydrolytic enzymes break down high molecular weight polymers to form biofunctional molecules during germination [67]. In recent research, germinated soy, broccoli, and purple rice all had anti-obesity benefits through the action of GM [68–70]. Although one study showed that germinated soy germ treatment could be a potential technique for obesity prevention by increasing weight reduction and treating obesity-related metabolic abnormalities, the authors did not analyze obesity-related gut-microbiota changes. The specific effects of the above studies on GM are shown in Table 4. As mentioned earlier, combining germination and fermentation could improve the functional activity of ordinary foods. Ren et al. showed that fermented germinated black tartary buckwheat with *Bacillus* sp. DU-106 resulted in a rise in tyrosine, lysine, total flavonoids, polyphenols, quercetin, and kaempferol in HFD-fed rats, alleviating hyperlipidemia and GM dysbiosis [71].

Table 4. Germinated food against obesity in vitro/in vivo based on gut microbiota.

Food	Experimental Results		Reference
	In Vivo/In Vitro	Gut Microbiota	
Broccoli seeds	Reduced WAT mass, the BW and adipocyte size	Increased the *Bacteroidetes*; decreased the *Firmicutes*/*Bacteroidetes*	[69]
Black Tartary buckwheat	Decreased the serum TC, TG, and LDL-C	Increased the *Lactobacillus*, *Faecalibaculum*, *Allobaculum* and decreased the *Romboutsia*	[71]

5. The Limitation of the Food-Derived Compounds in Modulating Gut Microbiota

Although the available data suggest sound effects of bioactive compounds derived from food in terms of gastrointestinal protection, there are, currently, insufficient data to draw definite conclusions due to the lack of human trials to corroborate in vitro findings. Diet directly impacts GM composition and metabolic activity because the undigested dietary residues provide substrates to GM [72]. The nondigestible food components, as colonic dietary substrates, can interact with the bacteria and epithelial cells in the colon, promoting the metabolism of colonic bacteria [73]. Most dietary polyphenols only exert biological activity when they reach the colon, while they are excreted from the body quickly [74]. The low absorption property and bioavailability of polyphenols from the gastrointestinal tract limits their modulatory effects on the GM. Bioactive peptides can regulate GM and can be utilized by the gut microbiota to produce corresponding metabolites. However, peptides may meet chemical, biological, and physical barriers by these cells after oral administration, reducing their impact on physiological processes [74]. As mentioned above, digestible carbohydrates also influence the GM, but many polysaccharide–gut microbe associations have evolved to be highly particular, while symbiotic bacteria enhance digestive physiology by offering an arsenal of various polysaccharide-degrading enzymes—which are mostly lacking in mammalian genomes [75]. In addition, as discussed above, the combination of different foods or compounds was used in obesity cases, based on improving GM (e.g., combining dietary fibers and phenolic compounds). However several studies indicated that certain combination of bioactive compounds, such as polyphenol and dietary fiber combinations or polyphenols and proteins, affected the bioavailability of bioactive compounds [76,77]. In summary, there are potential limitations for various nutrients (polyphenol, peptides, polysaccharides, etc.) and their ability to optimize GM in various metabolic diseases.

6. Combination of FMT and Dietary Compounds over Obesity

According to previous research, diet is a common and accepted strategy for regulating body weight, linked to gut microbiota changes. However, this regulation is a long-term and slow process. Recently, modulating GM has focused on FMT, a simple technique for transferring fecal bacteria from specified donors to receivers. As shown in Table 5, the donors are usually healthy lean adults or adult mice. Making fecal suspensions into capsules by freezing or gavage is a normal transplant method. As a result, the composition and function of the microbiome in recipients changed significantly, as listed in Table 5. It is considered an innovative, effective, and safe technique to treat challenging diseases like *Clostridium difficile* [78]. Subsequent researchers have looked into the possibilities of employing FMT in metabolic disorders [3]. Flexible use of diet and FMT intuitively proved the relationship between intestinal strains and obesity. Dietary adjustments with probiotic organisms and prebiotic substances can regulate bacterial development and FMT, whereas GM from healthy persons is injected into the gut. These are all viable therapies to shift microbiota and cure obesity [79]. The human gastrointestinal tract is a complex ecosystem; as such, ecological challenges to engraftment, such as microbiota resistance, competitive exclusion, and host environmental filtration, should be considered while conducting future FMT trials [80]. As shown in Figure 4, gut ecosystem resilience to invasion by new species may pose a challenge to successful FMT engraftment and minimize potential benefits to

metabolic parameters. Following FMT, a similar dysbiotic microbiota would likely be reselected if the overall host milieu was not addressed.

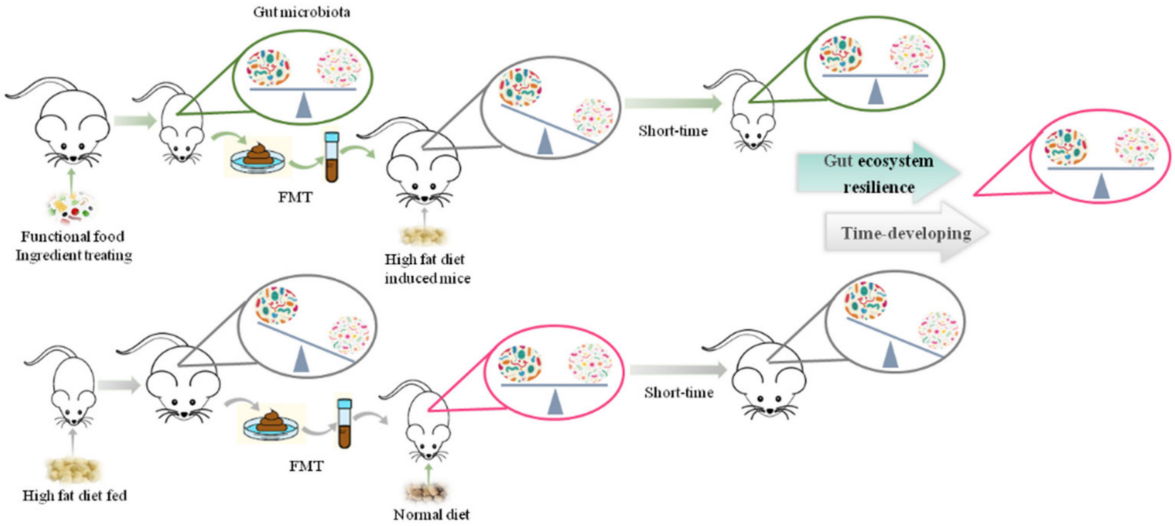

Figure 4. Combined FMT and diet are used and related challenges in obesity research. The green circles in the figure represent the balance of intestinal microbiota regulated by food functional ingredient or FMT. The gray circles in the figure represent the intestinal microbiota disorder in HFD-induced obesity mice. The pink circles in the figure represent the long-term stable gut ecosystem of the individual.

Functional compounds like resveratrol have significantly alleviated HFD-induced hepatic steatosis in mice. Subsequently, FMT was used to transfer microbiota from mice treated with bioactive compounds to mice fed by HFD; GM compositions in these mice were different from GM in HFD mice, but were identical to those of corresponding donor groups, providing evidence that resveratrol could alleviate hepatic steatosis through altering bacterial compositions [81]. Moreover, transplanting the resveratrol microbiota into HFD-fed mice was enough to reduce weight gain [82]. Other functional compounds, such as phenolic compounds and Ephedra sinica, combined with FMT on the development of obesity, were employed [83,84]. In conclusion, the combination of FMT and dietary compounds is a promising combination of fields that could compensate for the shortcomings of either treatment on their own.

Table 5. Summary of donor, recipients, delivery methods, and results in randomized, controlled trials of FMT for obese.

Donors	Recipients	Methods	Results	Reference
Healthy lean adults	Obesity adults with insulin resistance	Weekly oral capsule administrations	Improvement in metabolism after FMT among study participants with low baseline microbiome diversity.	[85]
A single lean donor	Obese without metabolic syndrome	Oral capsule administrations	Patients who received FMT had sustained shifts in microbiomes toward those of the donor; BAs profiles began to resemble the donor more closely.	[86]
Healthy individuals from Chinese Kazaks	*db*/*db* mice	Orally	*Desulfovibrio* and *Clostridium coccoides* levels were decreased, but the fecal *Akkermansia muciniphila* and colon histone deacetylase-3 protein expression were increased.	[87]

Table 5. *Cont.*

Donors	Recipients	Methods	Results	Reference
A single healthy lean donor	Obese metabolically healthy patients	FMT capsules	There was a change in glucose and insulin under the curve compared to baseline in the FMT group.	[88]
Four healthy same-sex lean donors	Adolescents with obesity	FMT capsules	Altered the gut microbiome's structure and function; two donor microbiomes dominated strain engraftment and were characterized by high *Prevotella*/*Bacteroides*.	[89]
Lean donor	Obesity patients with metabolic syndrome	Orally	Patients in the single-dose oral FMT combined with daily low-fermentable fiber group had significant improvements in HOMA2-IR.	[90]
Wild boar	Male C57BL/6N mice	Fecal suspension by oral gavage	FMT prevented HFD-induced obesity, lipid metabolism disorders; increased the *Lactobacillus* and *Romboutsia*.	[91]

7. Future Perspective

The emerging microbial metabolomics and proteomics implemented have provided scientific methods for understanding intestinal flora development in recent years. It is expected that the future research focuses will be as follows: the specific intestinal flora that plays a role in the treatment of obesity and the regulatory mechanism between the biological functions of flora in each region (cecum, colon, jejunum and ileum) should be studied to construct a correlation database between GM and different chronic diseases. Additionally, due to deep concerns regarding some beneficial bacteria, researchers should also focus on the regulatory mechanisms of harmful bacteria on. It will be necessary to develop the micro-ecological analysis technology for GM in the microbial genome. Researchers will also need to conduct research on structure and function at a micro-ecological level, provide reliable donor flora for clinical FMT, and improve the treatment efficiency of chronic disease patients through medical detection and construction of a fecal microbiota bank and fecal bacteria (biological) sample database that could be used for FMT.

8. Conclusions

This review investigated the body of literature on the basic mechanisms of obesity and the use of functional food ingredients to improve obesity. The etiology of obesity involved a complex interplay between genetic, environmental, lifestyle, dietary factors, and GM; some normal bacteria decreased and vanished, like the ratio of *Firmicutes* to *Bacteroidetes*, or microbiota-related products such as LPS, SCFA, BA. Dietary modification (using food-derived compounds like polyphenol, polysaccharides, alkaloids, and polypeptides) is essential in the prevention and treatment of obesity and related disorders. It could reduce HFD-induced BW, and lead to gut modulation showing beneficial effects. Recently, researchers also highlighted FMT, which involves the transfer of fecal microbiota from specific donors to recipients. FMT was used to reveal a relationship between changing GM and obesity. In the future, we could consider using FMT to treat other metabolic diseases, including obesity. Additionally, dietary and FMT treatment could also be an effective therapeutic method in reducing metabolic disorders. GM dysbiosis has seen improvement in a short time using only FMT. However, FMT is still in the scientific research stage and is thus subject to ethics, laws, and regulations in clinical practice when used in human or clinical treatment. Another issue is that the optimal size of fecal microbiota for treatment is still unclear. While promising, the influence of FMT on long-term clinical endpoints needs to be explored further.

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