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Exploring the role of bifidobacteria in obesity management: therapeutic application, modulatory mechanisms, and dietary strategies

Xiaodan Fu[a], Ying Yu[b], Haijin Mou[b], Ningyang Li[b], Xinmiao Ren[b], Shaoping Nie[a,*]

[a] *State Key Laboratory of Food Science and Resources, China-Canada Joint Laboratory of Food Science and Technology (Nanchang), Key Laboratory of Bioactive Polysaccharides of Jiangxi Province, Nanchang University, Nanchang 330047, China*

[b] *College of Food Science and Engineering, Ocean University of China, Qingdao 266003, China*

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ABSTRACT

The global rise in obesity and its associated metabolic syndrome has garnered significant attention in recent years. Targeting the gut microbiota has been proposed as a promising strategy for the treatment of obesity and its related metabolic disorders. *Bifidobacterium*, one of the typical intestinal microorganisms in healthy individuals, has been recognized for its beneficial role in maintaining overall health. Numerous animal and human studies have elucidated the beneficial impact of bifidobacteria in maintaining the physiological and metabolic well-being of the host. Previous studies have found that bifidobacteria play a crucial role in regulating intestinal microbial communities and metabolism, as well as alleviating obesity by managing appetite, improving insulin resistance, modulating cholesterol and lipid metabolism, reshaping immune marker levels, and reducing inflammation. However, there remains a lack of comprehensive exploration into the potential correlation between bifidobacteria and obesity. By exploring the link between bifidobacteria and obesity based on recent research, this review aims to provide a theoretical foundation for elucidating the fundamental mechanisms underlying probiotic bifidobacteria intervention and promote the therapeutic applications of targeted regulation of microbial communities for obesity treatment.

1. Introduction

Obesity, a chronic metabolic disorder, has rapidly increased worldwide since 1980, making it a prevalence challenge according to the Global Burden of Disease study[1]. Recent data indicates a rise in the global age-standardized average body mass index (BMI) in adults and an over 8-fold increase in the global age-standardized prevalence of obesity in children over the past 4 decades[2-3]. The alarming increase in obesity poses a significant threat to human health with increasing the risk of various metabolic disorders including hyperlipidemia, diabetes, and cardiovascular diseases[4]. Obesity is primarily reported to be an imbalance between calorie intake and expenditure, with emerging research suggesting that it is influenced by a multitude of factors. Research studies have identified environmental factors such as dietary patterns, early life conditions, endocrine disruptors, and inflammation status as potential contributors to the development of obesity[5].

The gut microbiota has increasingly recognized as a critical factor in maintaining host health, with recent researches unraveling the intricate interactions between the host and diverse microorganisms[6]. Changes of intestinal microbiota composition have been associated with numerous diseases such as obesity, inflammatory bowel diseases, hepatic steatosis, and various cancers, indicating potential disruptions in pathways related to glucose metabolism, energy metabolism, lipid metabolism, and immunity[7-8]. It has been demonstrated a link between intestinal microbiota and obesity and revealed that transferring healthy microbiota into adult germ-free mice resulted in elevated body fat content and insulin resistance[9]. Previous studies have indicated that a lower richness and diversity of gut microbiota may promote weight gain and the development of overweight

* Corresponding author at: State Key Laboratory of Food Science and Resources, NanchangUniversity, Nanchang 330047, China.
E-mail address: nie68@sina.com, spnie@ncu.edu.cn (S.P. Nie)

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conditions[10]. Furthermore, previous study revealed that introducing fecal microbiota from both lean and obese twins into separate groups of germ-free mice led to an increase in adiposity in the obese group, while the lean group maintained a lean phenotype[11]. Recent research has proposed potential mechanisms by which gut microbiota influences the development of obesity, including its role in energy extraction from the diet, regulation of satiety signal pathways, and modulation of gastrointestinal transit time[12]. Bacterial products play a crucial role in the development of obesity. Trimethylamine *N*-oxide (TMAO), an oxidized form of the microbial metabolite trimethylamine (TMA), has been shown to impact cholesterol conversion, leading to cholesterol accumulation and lipid metabolism disorders[13]. Imidazole propionate (ImP), a histidine-derived microbial metabolites, which has been shown to impair insulin signaling through the activation of the p38γ-mTOR1-S6K1 pathway[14]. Additionally, lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), bile acids (BAs), ethanol, and choline have been reported to modulate lipid metabolism in the liver and influence appetite regulation[15].

The gut microbiota has increasingly been recognized as playing a key role in mediating diverse metabolic functions between the external environment and host health. *Bifidobacterium* species are among the initial colonizers of the human intestine, with their abundance strongly linked to the overall health[16]. Bifidobacteria are anaerobic, Gram-positive microorganisms that are highly prevalent in the intestines of infants[17]. Randomized double-blind trials have provided compelling evidence supporting the efficacy of *Bifidobacterium* in combating obesity. Treatment with *Bifidobacterium* has been reported to reduce BMI, visceral fat accumulation, fat mass, and waist circumference in individual studies[18-19]. Given the potential beneficial effects on health, *Bifidobacterium* spp. have been extensively utilized in food field as active components[20]. Studies suggest that bifidobacteria significantly impact gut health by influencing microbial communities and modulate obesity through the regulation of appetite, insulin resistance, lipid metabolism, and chronic inflammation[5,16]. Besides, the development and application of bifidobacteria require careful consideration of long-term safety, the needs of vulnerable populations, and personalized nutrition strategies[16]. Despite these insights, the role of bifidobacteria in obesity management requires further detailed study. In this review, we will summary the recent studies and the correlation between *Bifidobacterium* and obesity, clarify the possible underlying mechanisms of *Bifidobacterium* treatment, and propose potential therapeutic approaches for targeted regulation of microbial communities in obese individuals.

2. Gut microbes and obesity

2.1 Gut microbiota composition in overweight and obesity

Obesity has emerged as a global pandemic, impacting over 650 million individuals and contributing significantly to morbidity rates. Recent research has highlighted the potential impact of gut microbiota in weight regulation[5]. Changes in the gut microbiota are observed in overweight and obese subjects (Fig. 1). Gut microbiota primarily consists of the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, among which Firmicutes and Bacteroidetes are predominant[6]. The abundance of Firmicutes is typically positively associated with obesity, as evidenced by studies showing that interventions such as Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, and dietary therapy have led to improvements in obesity accompanied by reductions in Firmicutes levels[21]. Research suggests that Firmicutes may contribute to increased energy extraction from the diet, with a negative correlation and observed between Firmicutes abundance and resting energy expenditure, as well as a positive correlation with fat mass[22]. Conversely, the abundance of Bacteroidetes tends to decrease in individuals with obesity, while low-calorie diet interventions have been shown to promote weight loss and restore Bacteroidetes levels in obese animal models[23].

Obesity resulting from high-fat or high-carbohydrate diets is positively correlated with an increased abundance of *Staphylococcus* and *Clostridium*, while levels of beneficial bacteria such as *Bacteroides*, *Akkermansia*, *Bifidobacterium*, *Butyrivibrio*, *Faecalibacterium*, and *Lactobacillus* are decreased[12]. *Methanogenic archaea*, commonly found in obese patients, can oxidize hydrogen (H_2) produced by Prevotellaceae. The increased H_2 utilization creates conditions for Prevotellaceae to efficiently ferment polysaccharides, leading to enhanced energy absorption in obese individuals[24]. Higher levels of *Staphylococcus aureus* have been consistently demonstrated to lead a low-grade inflammation in obese individuals[25]. Furthermore, typical *Clostridium* species have been reported to be positively associated with obesity through increasing energy storage and lipid synthesis[26]. A significant decrease in the abundance of Bacteroides in the intestines of obese individuals has been observed, with studies indicating the potential of Bacteroides in reducing the absorption of dietary fat[12]. *Akkermansia muciniphila*, a mucus-degrading bacterium, is recognized as a promising next-generation probiotic[27]. The presence of *A. muciniphila* is negatively correlated with body weight in humans and is reduced in obese individuals as well as in mice with type 2 diabetes[28]. Moreover, treatment with *A. muciniphila* has been demonstrated to improve metabolic profiles by preventing fat deposition, metabolic endotoxemia, and adipose tissue inflammation induced by a high-fat diet (HFD)[28]. The relationship between *Lactobacillus* and obesity is dependent on strain specificity. Specifically, *Lactobacillus reuteri* has shown a positive correlation with BMI, whereas *Lactobacillus paracasei* and *Lactobacillus plantarum* have demonstrated potential in preventing weight gain[29-30]. *Bifidobacterium*, a well-researched gut microbe, exhibits various beneficial physiological effects, including enhancing the intestinal mucosal barrier function, thereby preventing the transferring of harmful bacteria and promoting the growth of *Akkermansia*[18].

2.2 Changes of bifidobacteria in relation to obesity

Bifidobacteria, as a key intestinal microorganism closely linked to health, has received significant attention in its relationship with obesity. Accumulating research has shown a positive association between bifidobacteria and normal weight[22]. Calorie restriction has been demonstrated to prevent the development of metabolic syndromes. Calorie restriction-induced metabolic improvements, particularly in reduced body weight, were mediated by changes in the gut microbiota, with a significant increase in *Bifidobacterium* abundance[31]. In a study exploring different types of childhood obesity, *Bifidobacterium* spp. were found to be more abundant in healthy age-matched controls, suggesting that bifidobacteria could

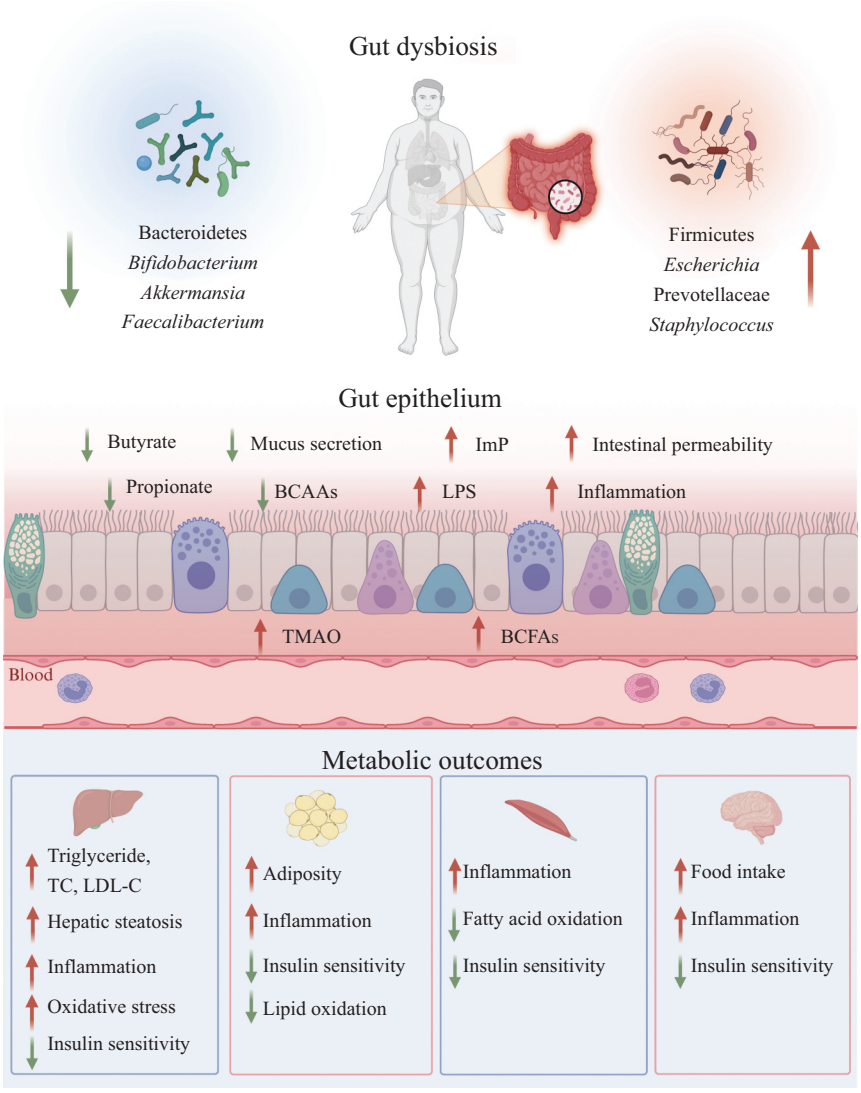

Fig. 1 Impact of gut microbiota on host metabolism related to obesity. Gut microbiota markedly affects host physiological functions, metabolic processes, and nutrient absorption, undergoing shifts associated with obesity variations in microbiota composition and metabolic activity, especially metabolite production, impact host physiology, metabolism, and immune responses. Upward and downward arrows in the figure indicate trends of increase and decrease, respectively. BCAAs, branched chain amino acids; BCFAs, branched chain fatty acids; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

serve as a potential marker for obesity[32]. Additionally, the abundance of *Bifidobacterium* was positively correlated with high-density lipoprotein cholesterol (HDL-C) concentration, which serves as an anti-atherosclerotic plasma lipoprotein and protective factor against coronary heart disease[33].

The insufficient presence of bifidobacteria in obese children may have originated during infancy, as higher levels of bifidobacteria were found in fecal samples of infants who maintained a normal weight compared to those who later became overweight[34-35]. *Bifidobacterium*, the predominant member of the infant microbiota, is likely be acquired through vertical transmission from the mother[17]. Studies have found reduced bifidobacterial abundance in overweight pregnant women compared to normal weight individuals, with BMI negatively correlated with bifidobacterial levels[36]. Consequently, lower abundance of bifidobacteria in infant gut intestine could induce an increased risk of obesity, whereas higher abundance of bifidobacteria during infancy may prevent the development of overweight[25,36]. There has been a global shift towards exploring bifidobacteria as promising probiotic dietary supplements, with an increasing emphasis on their application in the functional food industry. Nevertheless, the physiological features of bifidobacteria and the related mechanism need further systematically review.

3. Bifidobacteria as therapeutic strategy in the context of obesity

3.1 General features and safety

Bifidobacterium, a Gram-positive, strictly anaerobic genus from the Actinobacteria phylum, was first isolated from the feces of breastfed infants by Tissier and is now widely present in the gastrointestinal tracts of various animals, as well as in processed foods and other environments[16]. Total 138 taxa of genus *Bifidobacterium* has been discovered, with ongoing annual discoveries of new species and subspecies (LPSN, http://www.bacterio.net). Bifidobacteria, being among the earliest microorganisms to colonize the human gut

and persisting throughout the lifecycle[37]. Bifidobacteria dominate the infant gut microbiota, comprising up to 90% of the microbiota, and their abundance decreases with age[35]. Known for the probiotic properties, bifidobacteria are closely linked to health-promoting effects, primarily acclaimed for their capacity to enhance the well-being of the immune, nervous, and digestive systems[37].

The definition of probiotics as live microorganisms conferring health benefits on the host has evolved over time, with significant growth in clinical trials evaluating their efficacy and safety in the past 2 decades. Measurement advancements have played a crucial role in this expansion, emphasizing the need to assess both benefits and risks of interventions[20]. Multiple groups have provided valuable insights into probiotic safety. The United States Food and Drug Administration has proposed the Generally Recognized as Safe notice inventory, while the European Food Safety Authority has implemented the Qualified Presumption of Safety approach to aid in identifying safe microbial species[38]. Additionally, the best practices for probiotic quality and safety assessment have been consolidated with acknowledging the diverse regulatory frameworks across different regions globally[39]. Certain bifidobacteria species, widely utilized in dairy and various dietary supplements (Table 1), have garnered increased safety scrutiny for both environmental and human health concerns, particularly given the unpredictability of live microorganisms in foodborne diseases compared to food composition[16]. However, the development and application of bifidobacteria require careful consideration of several critical issues, including potential acute and long-term risks, the necessity for long-term studies, product quality, and special considerations for vulnerable populations, particularly infants and the elderly[20].

3.2 *Bifidobacteria as therapeutic target on obesity*

The escalating prevalence of obesity globally has elevated it to a rising risk of health. Long acknowledged for its significance in maintaining host health, bifidobacteria strains has garnered increasing attention[16]. Recent studies have illuminated the effect of gut microbiota structure and associated metabolites on obesity development. Amidst increasing acknowledgment of health-promoting properties of bifidobacteria, there has been a surge in research interest regarding their therapeutic potential in modulating obesity[18-19]. Clinical investigations assessing the impact and efficacy of bifidobacteria in obesity management have been conducted, as outlined in Table 2.

3.3 *Functional molecules involved in bifidobacteria-host interactions*

The health benefits of bifidobacteria, a significant group within the probiotic class, have been extensively researched and documented. Modulatory mechanisms, resembling those of other probiotic strains, include live bacteria, cell envelope components, the secretion of proteins, and microbial metabolites, all serving as mediators in microbe-host interactions. Exopolysaccharides (EPS) play a critical role in the interactions between bifidobacteria and their hosts. EPS obtained from *Bifidobacterium longum* 35624 induced host immunoregulatory responses and suppressed proinflammatory reactions[40]. Additionally, the EPS of *Bifidobacterium breve* UCC2003 has been implicated in modulating the early-life microbiota, potentially serving as a dietary substrate for the intestinal microbiota[41]. Bifidobacteria have elongated filamentous structures termed pili or fimbriae, which facilitate adhesion and interaction between the microbiota and the host[42]. Moreover, recent research highlights the role of extracellular bifidobacterial serpins of *B. longum* in microbe-host interaction by regulating eukaryotic signal pathways and inhibiting human intestinal serine proteases[43]. While molecules produced by bifidobacteria have been identified as participants in host-microbe interactions, the modulatory mechanisms employed by bifidobacteria on host health remains limited and need further investigation.

4. Modulatory mechanisms of bifidobacteria in obesity

The impact of bifidobacteria on obesity is mediated through diverse regulatory pathways, with an in-depth exploration of these mechanisms aiding in the development of personalized probiotic strategy. The underlying mechanisms of anti-obesity effects of bifidobacteria involve the modulation of appetite, energy metabolism, and lipid metabolism, as outlined in the following current research findings (Fig. 2).

Table 1
List of typical bifidobacteria strains used in commercial probiotics.

Species	Strain	Source	Institution	Intended use	Reference
B. animalis subsp. *lactis*	BB-12	Dairy cultures	Chr. Hansen, Inc., Denmark	Ingredient of conventional foods	[94]
	HN019	Yogurt	Fonterra, New Zealand	Ingredient of dietary supplements, fermented and non-fermented foods	[95]
	Bi-07	Healthy human	Danisco® DuPont, USA	Ingredient of dietary supplements	[96]
	IDCC 4301	Breast-fed infant feces	Ildong Bioscience Co., Ltd., Korea	Ingredient of conventional foods	[97]
	Probio-M8	Healthy breast milk	Inner Mongolia Agricultural University, China	Ingredient of dietary supplements	[98]
	V9	Intestines of healthy Mongolian child	Inner Mongolia Agricultural University, China	Ingredient of dietary supplements	[99]
B. bifidum	NITE BP-31	Human infant feces	Meiji Co., Ltd., Japan	Ingredient of non-exempt infant formula	[100]
	R0071	Intestine of healthy adult	Lallemand Health Solutions, Canada	Ingredient of powdered infant formula	[101]
	CCFM16	Human infant feces	Jiangnan University, China	Ingredient of dietary supplements	[102]
B. longum subsp. *infants*	R0033	Intestine of healthy infant	Lallemand Health Solutions, Canada	Ingredient of powdered infant formulas	[101]
	LMG 11588	Breast-fed infant	Nestlé Nutrition, New Zealand	Ingredient of formulas of infant and young children	[103]
	M-63	Healthy infant	Morinaga Milk Industry Co., Ltd., Japan	Ingredient of infant formulas and conventional foods	[104]
B. longum	BORI	Human infant feces	BIFIDO Co., Ltd., Korea	Ingredient of infant formulas and conventional foods	[105]
	BB536	Human infant feces	Morinaga Milk Industry Co., Ltd., Japan	Ingredient of term infant formula	[106]
B. breve	M-16V	Human infant feces	Morinaga Milk Industry Co., Ltd., Japan	Ingredient of infant formulas and conventional foods	[107]
	MCC1274	Human infant feces	Morinaga Milk Industry Co., Ltd., Japan	Ingredient of conventional foods	[108]

Table 2
Clinical investigations of anti-obesity effects of bifidobacteria stains.

Population	Intervention	Control	Duration (weeks)	Clinical findings	Reference
Healthy normal and overweight adults of BMI 23−30 kg/m^2 and age 29−64 years; intervention (n = 50); placebo (n = 50)	Capsules per day containing 1 × 10^{10} CFU *B. longum* BB536 and 5 × 10^9 CFU *B. breve* MCC1274	Placebo capsules per day without bifidobacteria	16	↓ Abdominal visceral fat area ↓ Total abdominal fat area ↓ Serum triglyceride levels	[109]
Adult volunteers of BMI 25−30 kg/m^2 and age 19–60 years; intervention (n = 51); placebo (n = 49)	Capsules per day containing 5 × 10^9 CFU *B. breve* B-3	Placebo capsules per day without bifidobacteria	12	↓ Body weight ↓ Waist circumference ↓ Hip circumference	[110]
Youths with obesity and insulin-resistance on diet of age 6−18 years; intervention (n = 51); placebo (n = 50)	Probiotic sachets per day containing > 2 × 10^9 CFU/AFU *B. breve* B632 and *B. breve* BR03 (1:1 mixture of the 2 strains)	Placebo per day without bifidobacteria	8	↓ Body weight ↑ Insulin sensitivity	[111]
Abdominally obese adults: Intervention (n = 86); placebo (n = 40)	1 capsule per day containing 1 × 10^{10} CFU *B. animalis* CECT 8145 or 1 × 10^{10} CFU heat killed *B. animalis* 8145	1 capsule per day of placebo (300 mg of maltodextrin)	12	↓Waist circumference ↓ Conicity index	[18]
Obese children age 10−15 years with insulin resistance; intervention (n = 23); placebo (n = 25)	Single-dose capsule per day containing 1 × 10^9−1 × 10^{10} CFU *B. pseudocatenulatum* CECT 7765	Placebo capsules per day without bifidobacteria	13	↓ BMI	[19]
Pre-obese adults of BMI 25−30 kg/m^2 and age 20−64 years; intervention (n = 40); placebo (n = 40)	Capsules per day containing 2 × 10^{10} CFU *B. breve* B-3	Placebo capsules per day without bifidobacteria	12	↓ Body fat mass ↓ Percent body fat	[112]
Overweight and obese adults of BMI 28.0−34.9 kg/m^2 and age 18−65 years; intervention (n = 168); placebo (n = 57)	1 × 10^{10} CFU/day *B. animalis* ssp. *lactis* 420 with/without Litesse® Ultra polydextrose 12 g/day	12 g/day of cellulose microcrystalline	24	↓ Body fat mass ↓ Waist circumference	[113]
Adult volunteers of BMI 24−30 kg/m^2 and age 40−69 years; intervention (n = 28); placebo (n = 24)	Capsules per day containing approximately 5 × 10^{10} CFU *B. breve* B-3	Placebo capsules per day without bifidobacteria	12	↓ Body fat mass ↑ Improvements of blood parameters related to liver functions	[114]

Note: AFU, active-fluorescent units; ↑ indicates rising; ↓ indicates declining.

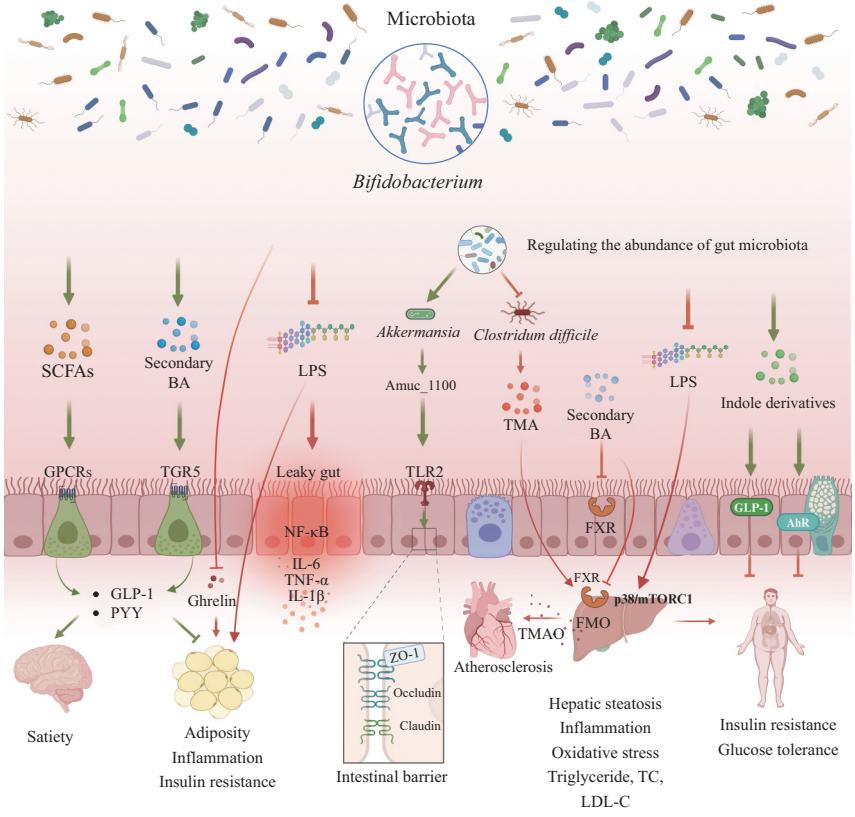

Fig. 2 Bifidobacteria-derived microbial messengers and related molecular mechanisms in the regulation of obesity and related symptoms. SCFAs produced by *Bifidobacterium* interact with G protein-coupled receptors (GPCRs), triggering the release of satiety hormones GLP-1 and PYY, thereby affecting insulin resistance and energy balance. *Bifidobacterium* restores dysregulated active ghrelin, a hormone regulating appetite and fat storage. Microbial-derived secondary BAs acting *via* Takeda G protein-coupled receptor 5 (TGR5) promote GLP-1 release and inhibit adiposity. *Bifidobacterium* inhibits increased LPS, thereby improving intestinal barrier integrity. Additionally, Bifidobacteria reduce TMAO levels by modulating intestinal microbiota composition, potentially by suppressing TMAO precursor-producing strains like *C. difficile*. Bifidobacteria have demonstrated efficacy in increasing *Akkermansia* levels, wherein the outer membrane protein Amuc_1100 enhances gut barrier integrity *via* Toll-like receptor 2 (TLR2). Bifidobacteria-derived metabolites such as indole and its derivatives bind to aryl hydrocarbon receptor (AhR), influencing the enteric nervous system and regulating GLP-1 release. FXR, farnesoid X receptor; FMO, flavin-containing monooxygenase; mTORC1, mechanistic target of rapamycin complex 1.

4.1 Satiety and insulin resistance

Feelings of hunger and satiety play an important role in driving feeding behaviours in both humans and animals. Loss of appetite control leading to overeating is a contributing factor to obesity. Research indicates that the administration of *Bifidobacterium* strains can help regulate food intake by influencing satiety-related hormone signal pathways[44]. The secretion of hormones has been indicated to be associated with the insulin-related signal pathways. Multiple studies have shown that both live and sterilized *Bifidobacterium* strains exhibit the ability to alleviate insulin resistance[45]. The impact of sleep deprivation on rhesus macaques was investigated and *Bifidobacterium* supplementation was observed to reduce body weight gain, mitigate abnormal glucose metabolism, and alleviate SD-induced insulin resistance[46]. Supplementation with *Bifidobacterium pseudocatenulatum* CECT 7765 was found to enhance insulin sensitivity and improve metabolic dysfunction associated with obesity in both mice and children[19,47]. *B. breve* B-3 was shown to enhance the gene expression related with insulin sensitivity in adipose tissues of the intestine and epididymis[48]. Adiponectin, a hormone which reduced level is observed in obese individuals, has the potential to reduce inflammatory cytokines and oxidative stress, thereby improving insulin sensitivity. Administration of *Bifidobacterium* was found to upregulate gene expression related to adiponectin synthesis in adipose tissues, leading to increased circulating adiponectin concentrations[8,49].

Leptin, a hormone involved in appetite regulation, is released by adipocytes and acts on the central nervous system to signal the energy balance status. In contrast, ghrelin, a hormone produced in the stomach, promotes appetite and food consumption, leading to fat accumulation, weight gain, and impacting glucose and lipid metabolism[50]. Studies indicated that *Bifidobacterium* treatment can modulate leptin levels. Animal models have been used to show a correlation between serum levels of leptin and ghrelin with the presence of *Bifidobacterium*. *B. longum* PI10 has exhibited probiotic effects in alleviating obesity, improving fasting glycemia, and addressing leptin resistance[51]. Upon analysis of the obese individuals, it was observed that *B. longum* APC1472 could normalize the dysregulated ghrelin levels associated with obesity[52].

Acetate generated by bifidobacteria has been shown to activate G-protein-coupled receptor 43 (GPR43) on intestinal L-cells, leading to the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which influence satiety by affecting the hypothalamus[53]. Intervention of *Bifidobacterium animalis* lactis GCL2505 has been reported to elevate acetate and GLP-1 levels[54]. Similarly, bifidobacteria strains isolated from breastfed infant fecal samples were capable of enhancing the activity of GLP-1[34]. The modulation of appetite is intricately linked to tryptophan and its derivatives, including indole and serotonin, which influence the enteric nervous system and subsequently regulate the release of GLP-1. Martorell et al.[55] demonstrated that *B. animalis* subsp. *lactis* (*B. lactis*) CECT 8145 influenced the satiety of *Caenorhabditis elegans* by targeting tryptophan metabolism with upregulating the neuropeptide signal pathway and modulating the serotonergic system, ultimately affecting the feeding behavior of *C. elegans*.

4.2 Energy expenditure and lipid metabolism

Obesity is characterized by an imbalance between energy intake and expenditure. *Bifidobacterium* has been indicated as a potential contributor for regulating energy metabolism, thereby offering improvements in obesity. Regulatory mechanisms have been reported, encompassing the modulation of fasting blood sugar levels, fat mass, lipid accumulation, and lipogenesis[8]. Accumulating studies showed that *Bifidobacterium* can modulate the expression of key genes involved in cholesterol and lipid metabolism, impacting cholesterol levels, and regulating the synthesis, transport, accumulation, and oxidation of lipid[5]. Furthermore, *Bifidobacterium* has the capacity to produce bile salt hydrolase (BSH), which aids in reducing the blood cholesterol levels of host. *B. longum* subsp. *infantis* YB0411 has been found to inhibit adipogenesis in 3T3-L1 pre-adipocytes by engaging in the regulation of the AMP-activated protein kinase (AMPK) pathway[56]. Studies collectively highlight the ability of *Bifidobacterium* to regulate both energy metabolism and lipid metabolism.

BAs, a group of amphipathic steroids that are synthesized in the liver and mostly altered by gut microbiota, are acknowledged for their role in the onset of obesity. BAs aid in the absorption of dietary fats in the intestines while also possess hormone-like properties through the stimulation of nuclear and membrane-bound receptors[57]. The signal pathways associated with BAs, which impact crucial physiological processes such as glucose metabolism, lipid utilization, and energy regulation, present promising avenues for therapeutic intervention in combating obesity[58]. Manipulation of microbiome composition and BA profiles, as well as their influence on intestinal health and immune responses. The genus *Bifidobacterium* is recognized for its possession of BSH genes. The consumption of probiotics or the higher abundance of resident bifidobacteria may potentially alter levels of secondary BAs in the gut microbiota[58]. Obese individuals were observed to exhibit elevated serum concentrations of primary BAs. Oligofructose-enriched inulin has been shown to prevent the natural rise of fecal primary BAs, possibly due to its promotion of increased *Bifidobacterium* levels[59]. The oral administration of commercial *B. longum* and *Bifidobacterium bifidum* was found to enhance BA signal, thereby promoting oxidative phosphorylation in adipose tissues, which led to reduced body weight gain, improved hepatic steatosis, and enhanced glucose homeostasis[49].

B. pseudocatenulatum CECT 7765 has been indicated to alter key regulators expression involved in fatty acid and cholesterol transport, as well as lipid biosynthesis[60]. Treatment of *C. elegans* with *B. lactis* CECT 8145 resulted in the upregulation of metabolic pathways involved in energy production and lipid metabolism including unsaturated fatty acid synthesis, fatty acid β-oxidation, and cholesterol metabolism[55]. Besides, *B. breve* B-3 induced upregulation of genes involved in fat metabolism in fat tissue in mice fed an HFD[48]. Treatment with *B. lactis* A6 improved obesity by enhancing mitochondrial biosynthesis and thermogenesis in adipose tissue. The underlying mechanism involved the promotion of fatty acid β-oxidation by *B. lactis* A6 through the regulation of related genes and proteins, including estrogen-related receptor α and uncoupling protein-1[61]. Furthermore, cell experiments indicated that the culture supernatant of *B. lactis* A6 stimulated fatty acid oxidation in 3T3-L1 cells, with acetate identified as a critical component that contributed to the fatty acid oxidation[61].

Microbial metabolites and gut peptides, including SCFAs and fasting-induced adipose factor, may play a role in improving metabolic syndromes through modulating gut microbiota[5]. Fasting-induced

adipose factor (FIAF), part of the angiopoietin-like protein family, serves as a circulating inhibitor of lipoprotein lipase, a crucial factor in microbiota-induced triglyceride accumulation in adipocytes[12]. In mice supplemented with *B. breve* B-3, a notable increase in *Fiaf* gene expression was detected in intestine, resulting in decreased adipocyte fat accumulation[48]. Metabolites produced by gut bacteria from dietary fibers, including acetate, lactate, and formate, have been demonstrated to influence carbohydrate and lipid metabolism[53]. Acetate has been indicated to improve mitochondrial function, reduce new fat production, and impact PPARα in the liver through the AMPK pathway, leading to increased gene expression associated with fat oxidation[62]. Administration of *B. lactis* GCL2505 suppressed body fat accumulation and enhance fatty acid oxidation in HFD-fed mice. Elevated plasma acetate levels were detected following GCL2505 treatment, along with inhibition of insulin signal in adipose tissues, resulting in heightened host energy expenditure *via* the activation of GPR43[54]. Lipoteichoic acid from *B. lactis* BPL1 also demonstrated a fat-reducing effect by regulating the insulin-like signal pathway, which is involved in ageing, immunity, and lipid metabolism[63]. The impact of *Bifidobacterium* on energy metabolism is also evident in its regulation of glucose metabolism. *B. pseudocatenulatum* CECT 7765 effectively reversed the effects of an HFD by modulating transcription and protein levels of glucose metabolism regulators[60].

4.3 Immune system and intestinal barrier

Obesity and related metabolic disorders are characterized by a chronic low-grade inflammatory response. Gut microbiota plays a crucial role in linking immune system to disease outcomes associated with obesity. Modulation of the gut microbiota through antibiotic or probiotic treatments can reduce metabolic endotoxemia, which triggers the low-grade inflammation[7,64]. Bifidobacteria have demonstrated the ability to interact with immune cells and influence specific pathways involved in both innate and adaptive immune responses[64].

Western-style diet has been shown to promote weight gain, hepatic fat accumulation, and signs of hepatic inflammation, including activating nuclear factor κB (NF-κB), which can be significantly alleviated by oral supplementation with *Bifidobacterium adolescentis*[65]. Similar beneficial effects were shown with *B. adolescentis* IM38 in ameliorating HFD-induced colitis[66]. In study involving patients with metabolic syndrome, *B. lactis* HN019 induced reductions in BMI and levels of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which are frequently linked to obesity-related inflammation[67]. *B. pseudocatenulatum* CECT 7765 mitigated obesity-linked inflammation in HFD-fed mice by rebalancing regulatory T cells and B lymphocytes and lowering pro-inflammatory cytokines associated with both adaptive IL-17A and innate immune responses[47]. In human trials, *B. pseudocatenulatum* CECT 7765 reduced inflammation in obese children by decreasing levels of high-sensitive C-reactive protein and monocyte chemoattractant protein-1, which are indicative of low-grade inflammation and early atherosclerotic plaque formation, respectively[19].

Intestinal choline can be converted to TMA, which is subsequently absorbed in the intestines, transported *via* the portal vein, and then enzymatically converted to TMAO by liver enzymes flavin-containing monooxygenases 1 (FMO1) and FMO3[33]. TMAO poses a risk factor for chronic illnesses. Moreover, bifidobacteria may combat certain strains like *Clostridium difficile* that produce TMAO precursor molecules[68-69]. Recent findings suggest that bifidobacteria exhibit the activity to reduce TMAO levels *in vivo*. *B. breve* Bb4, *B. longum* BL7, and *B. longum* BL1 were found to effectively lower plasma TMAO concentrations, restore gut microbial diversity, and maintain FMO activity in choline-fed mice[68]. Similarly, *B. lactis* F1-3-2 reduced plasma TMAO levels independently of FMO regulation, potentially attributed to its influence on the intestinal microbiota composition[69].

Researches have suggested that SCFAs are associated with the inhibition of MCP-1 expression and release, aiding in the anti-inflammatory response and improved intestinal barrier function by enhancing tight-junction integrity[70]. In various animal models of intestinal diseases, strains of *B. bifidum* and *B. longum* have shown promise in restoring immune markers in cases of chronic low-grade inflammation[71]. Treatment with *B. adolescentis* IM38 has been shown to enhance the expression of proteins crucial for maintaining tight junctions[66]. Besides, *Bifidobacterium* treatment promoted the restoration of mucus layer growth, thereby improving intestinal barrier function in Western-style diet-fed mice[72].

4.4 Regulation of intestinal micro-ecological environment

The human gastrointestinal system serves as a complex habitat for a diverse microbiota that has evolved to play a beneficial role in modulating host health. Numerous researches indicate that disruptions in the composition of intestinal microbiota, considered a crucial environmental factor, are linked to chronic diseases. Perturbations in the microbial ecosystem is related to the development of metabolic disorders such as obesity and diabetes mellitus[7].

The composition and metabolic functions of gut microbiota have been suggested to play a role in the development of obesity. Lower Bacteroides/Firmicutes ratio and reduced levels of beneficial bacterial strains such as *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* are typically observed with obese subjects[13]. *B. adolescentis* IM38 showed the capacity to inhibit HFD-induced LPS production by modulating the ratio of Proteobacteria to Bacteroides in the gut microbiota[66]. Daily consumption of *B. lactis* CECT 8145 has been shown to improve obesity, potentially through an increase in *Akkermansia* levels[18]. Besides, *B. pseudocatenulatum* CECT 7765 has been observed to restore HFD-induced imbalances in the intestinal microbiota, elevating *Bifidobacterium* abundance while reducing Firmicutes and Proteobacteria levels[47].

Genomics analysis revealed that *Bifidobacterium* possesses a strong ability to metabolize non-digestible carbohydrates. The production of oligosaccharides, monosaccharides, and SCFAs by *Bifidobacterium* can serve as substrates for other intestinal bacteria, thereby promoting the growth of beneficial bacteria, particularly those involved in butyrate production[12,53]. Treatment with *Bifidobacterium pseudolongum* was found to ameliorate diet-induced obesity while increasing gut microbiota diversity, the ratio of Bacteroides to Firmicutes, and the abundance of *Butyricimonas* and *Bifidobacterium*[73]. Similarly, *B. longum* subsp. *longum* also demonstrated the potential to reshape gut microbiota structure, including promoting the proliferation of *Roseburia*, a notable producer of butyrate, which is considered a

health marker that can impact colonic motility and immunity[74]. Additionally, bifidobacterial communities were observed to modulate the intestinal flora in mice, affect the production of SCFAs, and influence carbohydrate metabolism, which underscores the significance of *Bifidobacterium* in regulating the microecological environment of the intestine[75].

5. Dietary strategies for modulating bifidobacteria levels

Previous studies have highlighted the significant impact of bifidobacteria on the physiology of obese individuals, indicating that targeting bifidobacteria could be a promising strategy for obesity prevention and treatment. Given the current focus on cost-effectiveness and safety, dietary interventions emerge as a suitable method to promote the presence of bifidobacteria. Probiotics, prebiotics, and dietary options that have demonstrated efficacy in in promoting bifidobacteria growth and improving obesity outcomes (Table 3).

Targeted strategies focusing on increasing *Bifidobacterium* level in the gut microbiota hold potential as a viable approach for modulating obesity. Accumulating evidence suggests that the beneficial effects of prebiotics on host health are linked to modifications in gut microbiota, which in turn impact various pathological processes associated with obesity (Fig. 3). Studies have demonstrated the prebiotic properties of wheat-derived arabinoxylan oligosaccharides (AXOS) in obese individuals[76]. Supplementation with AXOS increased levels of intestinal PYY and GLP-1, improved inflammation,

Table 3
Dietary interventions enhance the abundance of intestinal bifidobacteria in obese subjects.

Intervention	Subjects	Variation of outcomes	Impact on gut microbiota	Reference
AXOS	C57BL/6J mice fed an HFD	Body weight gain and fat mass ↓ Hyperinsulinemia ↓ Insulin resistance ↓	*Bifidobacterium* ↑	[77]
MOS	C57BL/6J mice fed an HFD	Body weight gain ↓ Serum lipids ↓ Insulin resistance ↓	*Bifidobacterium* ↑ *Akkermansia* ↑ *Lactobacillus* ↑ *Mucispirilum* ↓	[115]
GOS	Western-type diet feeding C57BL/6 mice	Body weight gain ↓ Accumulation of epididymal and perirenal fat ↓ Insulin resistance ↓ Plasma cholesterol ↓	*Bifidobacterium* ↑ *Akkermansia* ↑ *Olsenella* ↓ *Alistipes* ↓	[79]
Inulin-type fructans	Adults with overweight/obesity	Appetite ↓ Body fat ↓	*Bifidobacterium* ↑	[80]
Oligofructose-enriched inulin	Children with overweight or obesity	Body weight *z*-score ↓ Percent body fat ↓ Serum triglycerides ↓	*Bifidobacterium* ↑ *Clostridium* ↓ *Bacteroides* ↓	[59]
Oligofructose	Sprague-Dawley rats fed a high sucrose diet	Body weight ↓ Body fat ↓ Insulin sensitivity ↑	*Bifidobacterium* ↑ *Lactobacillus* ↑ *Clostridium* ↓	[116]
AXOS and FOS	C57BL/6J mice fed a high fat/high sucrose diet	Body weight ↓ Adiposity ↓	*Bifidobacterium* ↑ *Butyricicoccus* ↑	[117]
Type 3 resistant starch from *Canna edulis*	C57BL/6J mice fed an HFD	Weight gain ↓ Metabolic inflammation ↓ Intestinal immunity ↑	*Bifidobacterium* ↑ *Roseburia* ↑	[118]
Whole grain Qingke	C57BL/6J mice fed an HFD	Body weight gain ↓ Glucose tolerance ↓ Serum lipid levels ↓	*Bifidobacterium* ↑ *Akkermansia* ↑ *Lactobacillus* ↑	[119]
Seabuckthorn polysaccharide	C57BL/6J mice fed an HFD	Body weight gain ↓ Serum lipid level ↓ Liver triglycerides level ↓	*Bifidobacterium* ↑ *Bacteroides* ↑ *Lactobacillus* ↓	[120]
Blueberry polyphenols	C57BL/6J mice fed an HFD	Body weight ↓ Adipose tissue weight↓	*Bifidobacterium* ↑ *Desulfovibrio* ↑ *Adlercreutzia* ↓	[86]
Polyphenol-rich extract of pomegranate peel	BALB/c mice fed an HFD	Serum level of cholesterol ↓ Inflammatory markers expression ↓	*Bifidobacterium* ↑	[87]
Red wine polyphenols	Caucasian adult obese patients	Triglycerides ↓ TC ↓ LDL-C ↓ HDL-C ↑ LPS ↓	*Bifidobacterium* ↑ *Lactobacillus* ↑ *Roseburia* ↑ *Escherichia coli* ↓ *Enterobacter cloacae* ↓	[121]
Dendrobium officinale dietary fiber	C57BL/6 mice fed an HFD	Glucose homeostasis ↑ Energy metabolism ↑ Serum low density/very low-density lipoproteins ↓	*Bifidobacterium* ↑ *Akkermansia* ↑ *Bilophila* ↓	[122]
L. plantarum ZJUFT17	C57BL/6J mice fed an HFD	Body weight gain ↓ Serum lipids ↓ Energy intake ↓	*Bifidobacterium* ↑ *Parabacteroides* ↑ *Olsenella* ↑ *Ralstomia* ↓	[82]
B. adolescentis IVS-1, *B. lactis* BB-12, and GOS	Obese adults (BMI of 30.0–40.0 kg/m^2)	Serum LPS, IL-1β, TNF-α ↓ Intestinal permeability ↓	*Bifidobacterium* ↑	[83]

Note: FOS, fructo-oligosaccharides; ↑ indicates rising; ↓ indicates declining.

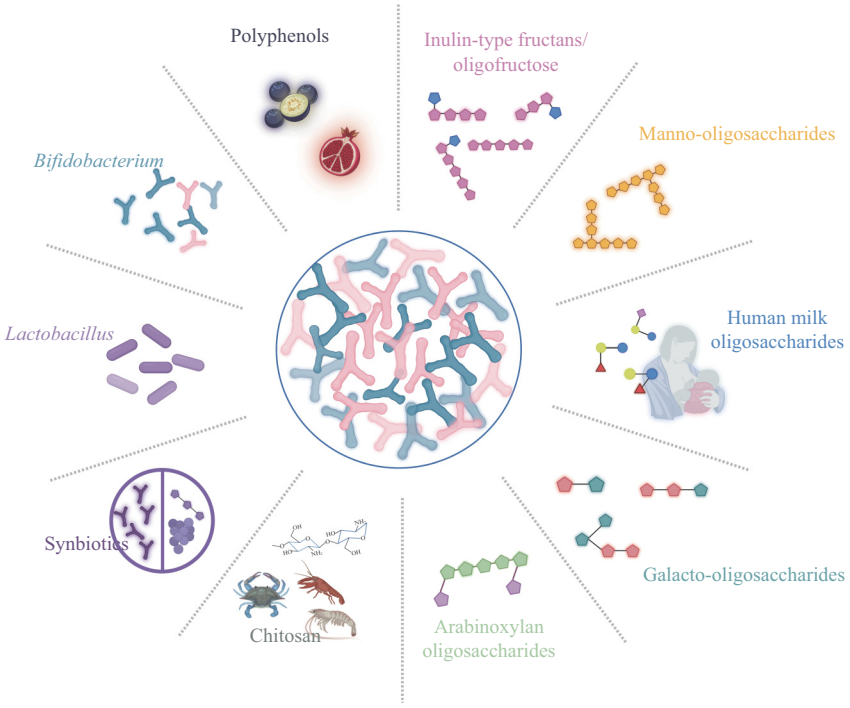

Fig. 3 Dietary strategies to enhance bifidobacteria levels for potential obesity alleviation.

and enhanced gut barrier integrity, coinciding with an augmentation in the population of bifidobacteria[77]. Manno-oligosaccharides (MOS), commonly used as a food additive, have also shown promise in increasing the abundance of *Bifidobacterium* and reduced body weight gain in obese mice[78]. Treatment with galacto-oligosaccharides (GOS) in mice following a Western-type diet led to a substantial rise in bifidobacterial abundance, consequently ameliorating syndrome-related parameters through reduced fat absorption[79]. Supplementation with oligofructose in obesity individuals has been reported to decrease body weight and serum triglyceride levels, while promoting the growth of bifidobacteria[80]. Human milk oligosaccharides (HMOs), the primary constituents of human milk, have been recognized for their selective promotion of bifidobacteria proliferation in breast-fed infants. Recent research has highlighted the ability of HMOs to rebalance the microbiota in dysbiotic adults while also promoting bifidogenic activity, suggesting a potential marker for obesity management[81].

Dietary supplementation with probiotics presents a viable strategy for enhancing bifidobacteria proliferation in the gut, thereby addressing obesity and inflammation by modulating serum metabolites and inflammatory cytokines[37,64]. Consistent findings were observed in research involving HFD-induced obese mice treated with *L. plantarum* ZJUFT17, which promoted the expansion of beneficial gut microorganisms, particularly *Bifidobacterium*, resulting in decreased serum levels of inflammatory cytokines and mitigation of metabolic syndrome[82]. Furthermore, administration of *B. adolescentis* IVS-1 and *B. lactis* BB-12 increased total bifidobacteria and enhanced gut permeability[83]. Synbiotics, including short-chain GOS, long-chain fructo-oligosaccharides, and *B. breve* M-16V, have also demonstrated protective effects against fat accumulation by promoting *Bifidobacterium* abundance in mice[84].

Utilizing natural products as a preventative measure against obesity represents an additional dietary intervention strategy to promote the *Bifidobacterium* abundance in the gut. Polyphenols, secondary plant metabolites with diverse biological activities, have been indicated to modulate BAs and restore gut microbiota dysbiosis, enhancing energy metabolism and preventing obesity[85]. Additionally, polyphenols extracted from blueberry and pomegranate peel have demonstrated effects on obesity by promoting beneficial gut microbiota, including *Bifidobacterium*[86-87]. Chitosan, a natural polysaccharide found abundantly in the shells of marine crustaceans, has been shown in studies to impact food intake, body weight, and fat accumulation, thereby aiding in preventing obesity[88]. Overall, complex carbohydrates, probiotics, and natural products provide effective strategies for enhancing the abundance of *Bifidobacterium* and potentially alleviating obesity.

Despite the importance of regulating gut microbiota for health management, the high individuality of microbiota presents challenges for achieving stable and optional modulation[89-90]. The gut microbiota composition in adults is highly variable among individuals, with considerable differences in the relative and absolute quantities at the genera and species level, further affecting the function and metabolism[91]. Hence, determining the composition and function of individual microbiota can aid in personalized nutrition strategies for precisely increasing bifidobacteria abundance[90]. Targeting the regulation of bifidobacteria, personalized nutrition has incorporated the application of probiotics, prebiotics, and synbiotics. Microbiome screening and sequencing techniques enable the selection of bifidobacteria strains that respond well to pro/pre/synbiotic applications, evaluate nutrition strategies based on personal microbiota profiles, and facilitate the development of personalized dietary strategies for obesity management[92-93].

6. Conclusions and perspectives

Treatment with *Bifidobacterium*, along with dietary polyphenols and complex carbohydrates, has been demonstrated to elevate intestinal bifidogenic activity sufficiently to attenuate systemic inflammation, enhance gut health, and contribute to host basal metabolism equilibrium, while concurrently fostering the proliferation of other beneficial microbes *via* diverse signal pathways. Targeted therapeutic interventions directed at modulating *Bifidobacterium* within the gut microbiota exhibit promise as a strategy for prevention and treatment of obesity and associated metabolic syndromes. This approach is anticipated to support further investigation into the functional roles of distinct species of *Bifidobacterium* within the gut microbiota, particularly concerning both obese and healthy individuals. Increasing number of studies indicate the favorable impact of probiotic consumption on lipid profiles enhancement and inflammation reduction, suggesting promising prospects for intervening in obesity and associated metabolic conditions. However, further research is required to definitively ascertain the effects of diverse *Bifidobacterium* strains or symbiotic preparation for both therapeutic objectives and health promotion.

Preclinical and clinical researches have consistently highlighted the association between *Bifidobacterium* levels and obesity. Studies suggest that bifidobacteria regulate appetite and improve insulin sensitivity through microbial metabolites such as SCFAs. Bifidobacteria modulate cholesterol and lipid metabolism in obese individuals by influencing BA metabolism, cholesterol synthesis, and the synthesis and oxidation of fatty acids. Additionally, the ability to reshape immune markers and reduce inflammation has been indicated with bifidobacteria treatment. Moreover, bifidobacteria confer benefits on increasing the abundance of beneficial gut bacteria such as *Akkermansia*, thereby regulating intestinal microbial communities and metabolism. Investigating the systematic regulatory mechanisms of *Bifidobacterium* in rodent models could provide essential insights for human research despite current ethical and practical limitations. With the widespread global use of bifidobacteria in food and supplements along with a growing understanding of the functional role of microbial communities, safety concerns regarding bifidobacteria have become increasingly prominent. While numerous international organizations have proposed various methods for assessing the safety of probiotics, reconsideration is necessary in light of emerging research data. In addition to the necessity for complete genomic sequencing of bifidobacteria strains, risks including pathogenicity and antibiotic resistance should be considered. Long-term assessment of probiotic safety is imperative due to the colonization of bifidobacteria strains in the host. Additionally, further research is needed to focus on regulating obesity by bifidobacteria in specific populations, particularly pregnant women, adolescents, children, and individuals with immune dysfunction.

Enhanced microbiome-diet investigations and focused screening of *Bifidobacterium* strains are essential for refining strategies aimed at designing optimal strain mixtures with specific functions and dietary components to support strains colonization, effectively regulate intestinal *Bifidobacterium* populations, thereby promoting human health. The increased data on the application of *Bifidobacterium* strains in relation to human health, coupled with clinical and animal studies, is expected to illuminate the factors influencing specific *Bifidobacterium* compositions and aid in the development of targeted microbiota-based strategies for addressing obesity and related metabolic conditions. While considerable progress has been made in understanding the impact of gut microbiota on host health, it is crucial to differentiate between causation and correlation in research studies to effectively design interventions targeting the gut microbiota or utilizing bioactive compounds. Given the individual variability in gut microbiota composition and function, personalized dietary strategies are necessary. Reported pro/pre/synbiotic applications combined with sequencing technology provide approaches for personalized gut microbiota modulation for obesity management. Predictive analytics combined with microbiome data will facilitate the practical application and safety of personalized dietary approaches. Personalized application of *Bifidobacterium* strains is poised to play a pivotal role in the future of medical and nutritional strategies for the prevention and treatment of obesity.

Conflicts of interest

Shaoping Nie is an editorial board member for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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