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Research Article

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Probiotic *Bifidobacterium* Lactis Combined with *Lactobacillus Plantarum* Effectively Reduced Weight and Intestinal Microbiota

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Abstract
Probiotics intake can ameliorate body weight and fatty liver development. The fruit and vegetable also performed anti-inflammation effects. The fermented vegetable solid drink (FVSD) was combined fruit and vegetable with probiotics and further examining the anti-obesity efficacy in this study. The FVSD promote lipolytic activity effect was examined on OP9 cells and the anti-inflammation effect was performed via Q-PCR analysis on C2BBe1. To investigate the weight management potential and gut microbiota influence. The obese subjects were recruited, and then performed anthropometric measurement and next-generation sequencing (NGS) after FVSD intervention. In the results, the lipolytic activity effects were significantly increased and the LPS induced inflammation response was significantly reversed by FVSD co-treatment. After FVSD administration, obese subjects were significantly ameliorated body weight, body fat weight, and body fat at 4 weeks. And the waist-to-hip ratio was improved at 8 weeks. Both aspartate aminotransferase (AST), alanine aminotransferase (ALT) were significantly improved with anti-fatty liver potential. The NGS analysis suggested FVSD intervention could increase Christensenellaceae and Parabacteroides abundance of subjects' gut microbiota. In conclusion, FVSD performed a great anti-obese effect in vitro and in vivo.

Keywords: Bifidobacterium, Lactobacillus, Probiotics, Weight reduction.

Introduction
Obesity is a global epidemic and is considered to cause serious chronic diseases such as hypertension, cardiovascular disease, diabetes, cancer [1]. The current strategy is to fight obesity diet control, exercise, medication and surgery, but diet and exercise do not continue to strictly, and enforce the adverse side effects of drugs also limits its therapeutic use [2]. Fortunately, most recently about some interesting research on obesity is helping to validate this new method of medical disease control.

Obesity can lead to a change in the composition of the intestinal microbiota [3]. The main types of bacteria in the intestinal microbiota are *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria,* and *Verrucomicrobia* [4]. The intestinal microbiota can regulate the metabolism of the host, including weight control. In animal and human studies, it has been found that the composition of the intestinal microbiota related to obesity [5]. The study showed that through gene sequence analysis, it was found that intestinal bacteria such as *Bacteroidetes* and *Firmicutes* were colonized [6]. Weight loss makes the ratio of *Bacteroidetes* to *Firmicutes* up regulated in humans [7]. Thus, changes in the intestinal microbiota, may be a novel strategy for the treatment of obesity.

Recent studies had demonstrated that probiotic strains play an important role in modulating immune responses and exert anti-obesity effects [8]. *Bifidobacterium* was one of the most abundant probiotic bacteria in the intestine of mammals [9]. Studies had shown that *Bifidobacterium* can inhibit the absorption of cholesterol in the small intestine, and *Bifidobacteria* are believed to improve metabolism-related diseases, including reducing insulin resistance, fat accumulation, and fatty liver [10, 11]. *Lactobacillus* probiotic has many functions, can reduce blood fat, protect the cardiovascular system and reduce obesity [12]. *Lactobacillus rhamnosus, Lactobacillus brevis*, *Lactobacillus plantarum* and *Lactobacillus paracasei* had lipid-lowering effects, which can reduce body weight and increase metabolism [13]. In addition, *Lactobacteria* and *Bifidobacteria* suppressed weight gain of mice fed a high fat diet [14]. Therefore, specific strains of *Lactobacteria* and *Bifidobacteria* may be potential therapeutic candidates for anti-obesity.

In this study, we used fruit and vegetable powder with TCI604 (*Bifidobacterium lactis*) and TCI507 (*Lactobacillus plantarum*) to make a solid drink (FVSD). We used solid beverages to examine whether it increased fat metabolism and reduced intestinal inflammation. At the same time, we recruited obese subjects and taking solid beverages for 8 weeks to examine whether it decreased weight, and regulated intestinal microbiota.

Materials and Methods

Lipolytic Activity Assay

8×10^4 OP9 cells were seeded with 500 µl pre-adipocyte expansion medium in 24 wells. And incubated at 37 ℃ for 7 days and replace with a fresh differentiation medium every other day. After 7 days, observe lipid droplet formation using microscopy to make sure the cells are fully differentiated. Add 0.25% of FVSD and incubate for another 7-10 days and change the medium every other day. And proceed to the glycerol content analysis (Cayman: Item No.10010755). Then collect cell culture supernatant from each well, and then transfer 25 µl of cell culture supernatant from each well and standard into a new 96-well plate. Add 100 µl of reconstituted free glycerol assay reagent per well. After 15 minutes at room temperature and further measuring at 540 nm.

Inflammation Related Genes mRNA Expression Analysis

1.5×10^5 C2BBe1 cells in 2 ml of the media with 0.25% of FVSD were seeded in each well of 6-well plates and incubated for 24 hours. And change the medium with or without lipopolysaccharide (LPS) and FVSD for examining inflammation-related gene expression. Then, we collected the cells and used the RNA extraction kit for RNA collection. Finally, we adjusted the RNA concentration to 75 ng/µL for mRNA expression analysis. The IL-1β, IL-8, IL-18, and TNF-α mRNA expression level was analyzed by qPCR.

Clinical Trial

This clinical study was approved by the ethics committee of the Antai Medical Care Corporation Antai Tian-sheng Memorial Hospital (IRB No. 20-039-A), and the study protocol was registered with the ClinicalTrials.gov (NCT04501601). All methods were performed following the relevant guidelines and regulations. 25 adult subjects were recruited, and informed consent was obtained from all subjects before the study.

Subjects consumed daily solid drink for 8 weeks, and recorded weight, body fat, waist-to-hip ratio at 0, 4, and 8 weeks. In blood analysis, liver function indicators were analyzed at 0, 4, and 8 weeks, the fecal samples were obtained from subjects at weeks 0, 4, and 8. and intestinal microbiota was also analyzed through next-generation sequencing (NGS). Inclusion criteria included: i) age over 20 and below 60 years old; ii) body mass index (BMI) ≥ 24 or body fat > 25% (male) and body fat > 30% (female); Exclusion criteria included: i) Women who are breastfeeding, pregnant and menopause. ii) History of serious diseases associated with heart, liver, kidney, endocrine systems or other organs; iii) Type 2 diabetes or performed other weight loss methods within six months, including diet control, exercise, drugs; iv) drug consumption, alcohol addiction, gastrointestinal diseases.

Test Sample

The main ingredients of solid beverages were fruit and vegetable powder, *Bifidobacterum lactis* (TCI604) and *Lactiplantibacillus plantarum* (TCI507), water. Each subject was required to consume daily solid drink before lunch for 8 weeks. The test sample is a pack of 13 grams, which is melted with 180 ml of 45°C water before consumption.

Statistical Analysis

All values were expressed as mean ±SD between sample populations differences statistical result was determined by an unpaired two-tailed Student's t-test. Statistical significance was considered at P value < 0.5.

Results

FVSD increased the Lipolytic Activity and Decreased Inflammation in Vitro

First, in order to examine whether FVSD increased lipolytic activity, using the mouse embryonic stem cells derived stromal cells, OP9. The OP9 was differentiated into adipocytes, and treated with FVSD, then examined the glycerol content. Triglyceride was digested by lipases, and converted into fatty acid and glycerol [15]. We found that solid drinks could increase glycerol by about 121.5% (Figure 1). This result revealed that FVSD increased lipolytic activity. Second, in order to explore whether FVSD decreased intestinal inflammation, we used the human-derived colorectal cells, C2BBel, and using lipopolysaccharides (LPS) to mimic inflamed environment, and treated with FVSD, then examined inflammation related gene expression. We found that IL-1β, IL-8, IL-18, and tumor necrosis factor-alpha (TNF-α) were increased in LPS stimulation. Conversely, as LPS combined with FVSD treatment, the IL-1β, IL-8, IL-18, and TNF-α were decreased by 31.4, 2.1, 3.3, and 10.6 fold respectively (Figure 2). This result suggested that FVSD treatment could ameliorate the intestinal inflammation response.

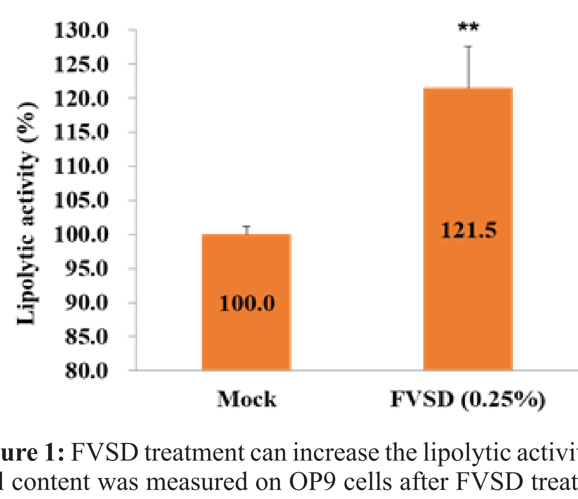

Figure 1: FVSD treatment can increase the lipolytic activity. Glycerol content was measured on OP9 cells after FVSD treatment. (n = 3; mean value ± S.D.) (*p < 0.05; **, p < 0.01; ***, p < 0.001).

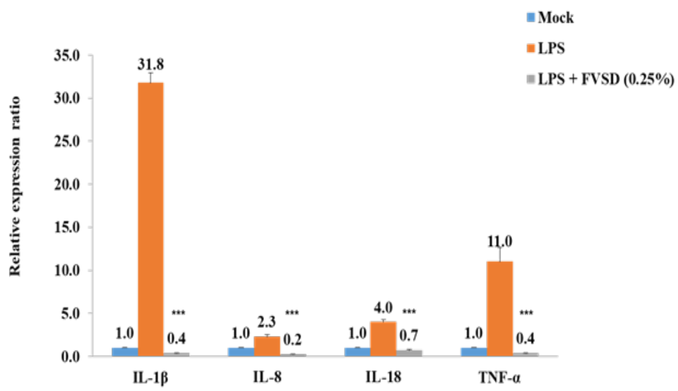

Figure 2: FVSD treatment can reverse LPS-induced inflammation related genes induction on C2BBel. (n = 3; mean value ± S.D.) (*p < 0.05; **, p < 0.01; ***, p < 0.001).

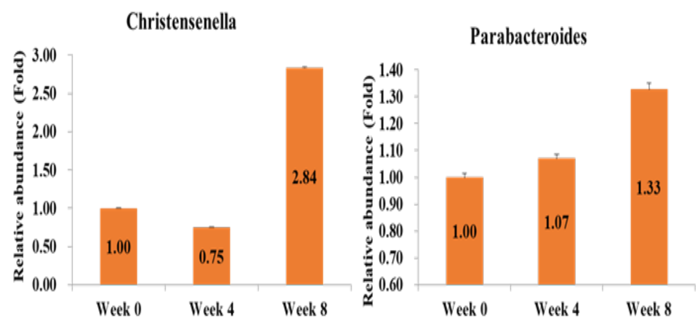

Figure 3: FVSD can ameliorate obesity through regulating the intestinal microbiota of obese subjects. Christensenella and Parabacteroides abundance were increased after FVSD administration by NGS analysis. (n = 25; mean value ± S.D.)

FVSD had Anti-Obesity Effect in Obesity Subjects

To further explore the weight management efficacy of FVSD in a clinical trial. A total of 25 obesity subjects were recruited and administrated FVSD daily for 8 weeks and examined at weeks 0, 4, 8 weeks. Table 1 showed the results of anthropometric measurements before and after the study. After 4 weeks of FVSD intervention, the result of body weight, body fat weight, and body fat performed significantly improvements in comparison with week 0. Follow up to the week 8 result, the body weight, body fat weight, body fat was significantly improved. Besides, the waist-hip ratio (WHR) also performed significantly improved at week 8 intervention.

Table 1: Results of anthropometric measurements. (N= 25; mean value ± SD). *p < 0.05; **, p < 0.01; ***, p < 0.001 (significant difference between week 0 and week 4 or week 8 after FVSD administration)

Subjects (n=25)	Group	Mean±SD	P-value	Significancy
Bodyweight (kilogram)	Week 0	80.7±15.7		
	Week 4	79.5±15.2	p<0.001	***
	Week 8	78.6±14.9	p<0.001	***
Body fat weight (kilogram)	Week 0	29.9±6.5		
	Week 4	28.5±6.2	p<0.001	***
	Week 8	27.9±6.3	p<0.001	***
Body fat (%)	Week 0	37.4±6		
	Week 4	36±6	p<0.001	***
	Week 8	35.8±6	p<0.001	***
Waist-hip ratio	Week 0	0.9±0.1		
	Week 4	0.9±0.1	0.098345	
	Week 8	0.9±0.1	p<0.01	**

FVSD Improved Fatty Liver in Obese Subjects

To examine whether the FVSD administration decreased fatty liver, obesity subjects were examined aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin. ALT and AST was known as indicator enzymes of the presence of liver disease. Elevated AST or ALT was associated with fatty liver [16]. When liver cells were damaged, the albumin content decreased [17]. The table 2 showed the results of biochemical analysis before and after FVSD intervention. As a result, both AST and ALT were performing a decreasing trend. In static results, the AST was decreased significantly, but ALT was not, suggesting FVSD improved fatty liver in obese subjects.

Table 2: Results of biochemical analyses. (N= 25; mean value ± SD). *p < 0.05; **, p < 0.01; ***, p < 0.001 (significant difference between week 0 and week 4 or week 8 after FVSD administration)

Subjects (n=25)	Group	Mean±SD	P-value	Significancy
AST/GOT (U/L)	Week 0	24.1±12.7		
	Week 4	20.2±7.1	p<0.01	**
	Week 8	19.2±11.0	p<0.01	**
ALT/GPT (U/L)	Week 0	31.2±27.8		
	Week 4	27.1±18.9	0.062505	
	Week 8	25.5±17.8	0.087481	
Albumin (g/dL)	Week 0	4.5±0.3		
	Week 4	4.7±0.3	p<0.001	***
	Week 8	4.6±0.3	0.179296	

FVSD Improved Intestinal Microbiota in Obese Subjects

To investigate whether FVSD regulated intestinal microbiota in obese subjects, we examined microbiota from subjects' feces by next generation sequencing (NGS). The *Christensenellaceae* and Parabacteroides on decreasing weight gain, hyperglycemia, and hepatic steatosis in high-fat diet (HFD)-fed mice [18]. In figure 3, both of *Christensenellaceae* and *Parabacteroides* related abundance were increased after FVSD intervention. The *Christensenellaceae* was increased by 2.84 fold and the *Parabacteroides* was increased by 1.29 fold. The results suggested that FVSD could ameliorate obesity through regulating the intestinal microbiota of subjects.

Discussion

In this study, we found that FVSD increased the lipolytic activity and decreased inflammation in vitro, as well as, FVSD decreased body weight, improved fatty liver, and regulated intestinal microbiota in clinical trial. FVSD contained two major bacteria, including TCI604 (*Bifidobacterium* lactis) and TCI507 (*Lactobacillus plantarum*). Studies showed that *Lactobacteria* and *Bifidobacteria* can inhibit weight gain in high fat diet induced mice [19]. *Bifidobacterium* longum exhibited a more significant effect in lowering serum total cholesterol [20]. *Lactobacteria* can inhibit cholesterol synthase, thereby reducing the production of cholesterol, and *Bifidobacteria* promote the elimination of cholesterol in feces [21]. Consistent with our results, FVSD can increase the fatty acid breakdown. Probiotic treated-mice improved glucose-tolerance, and decreased inflammatory cytokines [22]. *Lactobacteria* was shown to adhere to intestinal epithelial cell line and had anti-inflammation in vitro. *Bifidobacteria* and *Lactobacteria* can produce superoxide dismutase (SOD), reduced inflammatory cytokines IL-1β, TNF-α, and improved intestinal conditions [23]. *Bifidobacteria* interfere with pro-inflammatory signals upstream of the pathway of NF-κB activation for LPS and TNF-α [24]. Consistent with our results, FVSD decreased the inflammation-related gene induction by LPS.

Probiotic supplement resulted in *signifcant* reductions in body weight, BMI, waist circumference and waist-to-height ratio [25]. *L. plantarum* and *L. gasseri* reduced the body weight, and cholesterol level. The *Lactobacteria* was showed lowering effects on abdominal adiposity, body weight, suggesting its beneficial influence on metabolic disorders [26]. Multi-strain probiotic contained *Lactobacteria* and *Bifidobacteria* can reduce BMI, body weight and WHR in overweight/obese adults [27]. Consistent with our results, FVSD decreased body weight, body fat weight, and WHR. Some probiotics can inhibit TNFα and enhance adiponectin to improve the intestinal microbiota, leading to regulation of blood sugar, lipid metabolism and protection of the liver [28]. *Bifidobacterium*, *Lactobacillus*, had shown beneficial effects in rodent models of nonalcoholic fatty liver disease (NAFLD). Some studies indicated that activating the Nrf2/ARE pathway had a hepato-protective effect [29]. *L. plantarum* caused the activation of Nrf2 in liver, thus alleviating oxidized oil induced hepatic injury in mice [30]. Short-term oral supplementation with *B. bifidum* and *L. plantarum* can decrease AST, ALT activity, and regulated bowel flora [31]. Consistent with our results, FVSD decreased AST, ALT expression.

The gut microbiota appeared to play a role in the pathogenesis of obesity and associated diseases. The relative abundance of *Christensenellaceae* in the human gut is inversely related to host BMI [32]. *Parabacteroides* reduced obesity was associated with increased adipose tissue thermogenesis, and reduced inflammation and insulin resistance in HFD-fed mice [8]. In the oral *Bifidobacterium* treatment group, *Christensenellaceae* continued to increase [33]. The intake of *Bifidobacterium*, *Lactobacillus* can increase *Christensenellaceae* or *Parabacteroides* [33]. Consistent with our results, FVSD increased *Christensenellaceae* or *Parabacteroides.* In addition, we also found that FVSD decreased *Eggerthella, Clostridium, Acinetobacter* (data not shown).The possible mechanism was that branched chain fatty acids (BCFA), especially isobutyric acid and isovaleric acid, affected human fat cells by inhibiting lipogenesis and glucose metabolism [33].

Conclusion

This study showed that solid drinks containing probiotics *Bifidobacterium*, *Lactobacillus* supplementation could increase the lipolysis process and reduce intestinal inflammation. In clinical trials, it was found that obese subjects had a significant reduction in body weight, body fat, and waist-to-hip ratio after taking it for 8 weeks. And it had been observed that it can improve liver function indicators and reduced the fatty liver. It was further discovered that after 8 weeks of taking it, it can increase the beneficial bacteria in the intestines and improved fat metabolism, such as increasing *Christensenellaceae*, *Parabacteroide*. Although the detailed mechanism was not yet clear, more studies were needed to confirm, but this study proposed a new weight reduction strategy, using the combination of probiotics to regulate the intestinal flora and achieved the anti-obesity effects [34, 35].

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