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Review Article

Prophylactic Efficacy of Butyrate Fermented in *Aloe vera* Gel to Obesity-Prone Subjects Case Reports: Children-Growth Supported with *Aloe vera* Juice Ingestion

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Abstract

The gut microbiota-derived metabolite and fermented butyrate in *Aloe vera* gel as a protective factor against pediatric obesity and obesity-prone adults were discussed. The efficacy of butyrate as the central role of a healthy diet and gut microbiota function to achieve an optimal endogenous production was highlighted as an adjuvant.

In case reports we expressed children-growth supported with *Aloe vera* juice ingestion.

Keywords: *Prophylactic Efficacy; Butyrate Fermented; Aloe vera Gel; Obesity*

Introduction

Obesity is a chronic disease that results in substantial global morbidity and mortality. The increased prevalence of obesity these days has drawn attention to the worldwide to be over-weight or obese. The latest data from the National Health and Nutrition Examination Survey show that the prevalence of obesity among US children and adolescents was 18.5% in 2015 - 2016. Overall, the prevalence of obesity among adolescents (12 - 19 years; 20.6%) and school-aged children (6 - 11 years; 18.4%) was higher than among preschool-aged children (2 - 5 years; 13.9%). School-aged boys (20.4%) had a higher prevalence of obesity than preschool-aged boys (14.3%). Adolescent girls (20.9%) had a higher prevalence of obesity than preschool-aged girls (13.5%) [1]. A higher prevalence of obesity than preschool-aged was determined to be the participants with more than an average body mass index (BMI) of 30 by World Health Organization (WHO), and 25 by Japan Society for the Study of Obesity (JSSO). Ma., *et al*. [2] investigated that the increased body weight (Body mass index) or central obesity (A waist circumstance) were associated with a higher risk of developing dementia in a representative sample of English adult subjects. These findings have significant implications for dementia prevention and overall public health.

Natural products can be very effective in the prevention of obesity-related disorders. The anti-obesity effects of *Aloe vera* gel administration at 100 mg and 200 mg/kg/day, in diet-induced obesity rat model, and *Aloe vera* gel reduced fat accumulation via its protective

role against obesity-related metabolic alterations and antioxidant effects. *Aloe vera* has great potential as functional foods in the activation adipose lipolysis and the prevention of obesity-related metabolic alteration. *Aloe vera* gel could be recommended as a natural treatment to correct obesity-related alterations [3]. Protective effect of *Aloe vera* gel polysaccharide (Aps) on pancreatic ß-cells in response to free fatty acids (FFA) was determined using hamster pancreatic ß-cell line HIT-T15 by Kim [4] was found that the anti-apoptotic properties of Aps were largely due to the relief of endoplasmic reticulum (ER) stress signaling. Aps were effective in interfering with the FFA-induced activation of the PERK and IRE-mediated pathways as well as reactive oxygen species generation, thereby protecting pancreatic ß-cells from lipo-toxicity. After oral administration of Aps, markedly lowering fasting blood glucose levels were observed in db/db mice, providing evidence of the potential of Aps as an alternative insulin sensitizer. Therefore, it seems that Aps have a protective effect against type 2 diabetes by modulating obesity-induced ER stress in pancreatic ß-cells.

Present review exhibited prophylactic efficacy of *Aloe vera* gel and its fermented butyrate to obesity-prone subjects. In case reports, growth of children showed a possible participation of *Aloe vera* juice in long term-ingestion, suggesting the epigenetic roles of fermented butyrate in Aps [5].

In vitro and *in vivo* anti-obesity efficacy of Aloe vera

Medicinal plants have been examined to for their anti-obesity effects, including *Aloe vera*. Yunusoglu., *et al*. [6] aimed to elucidate the inhibitory effect of *Aloe vera* extract on adipogenesis. Firstly, 3T3-L1 pre-adipocytes were stimulated so as to differentiate into mature adipocyte using adipogenic differentiation cocktail consisting of 10 µg/mL insulin, 0.5 mM isobutylmethylxanthine, 0.25 mM dexamethasone, and 100 ng/mL biotin on day 0. Various concentrations (10 - 50 g/mL) of *Aloe vera* extract with no cytotoxic effect were applied to differentiated 3T3-L1 cells. Glyceraldehyde-3-phosphate dehydrogenase (GPDH) activity, Oil red O staining, intracellular triglyceride levels, and gene expressions of transcription factors and lipolysis-associated gene were examined in order to investigate the effect of *Aloe vera* extract on adipocyte differentiation. *Aloe vera* treatment caused a continuous decrease in cell size and intracellular triglyceride accumulation. Despite the fact that GPDH activity, mRNA levels of transcription factors and lipolysis-associated genes decreased in mature adipocytes treated with *Aloe vera* extract. These results suggest that *Aloe vera* may have a therapeutic effect in prevention and/or treatment of adipogenesis-related obesity.

Aloe vera fermented beverage intervention alleviates lipid accumulation and the complications of obesity in high-fat-diet mice

The effects of *Aloe vera*-fermented beverages (AFB) on obesity and its complications were studied on HepG2 cells in high-fat environment and high-fat diet (HFD) mice by Fu., *et al*. [7]. The author found that AFB intervention decreased the amount of lipid droplets of HepG2 cells, suppressed the body weight gain and adipose accumulation, and reduced the serum contents of total cholesterol, alanine aminotransferase, and interleukin 10 of HFD-mice. In addition, it also changed the composition of the gut microbiota. The ratio of *Firmicutes/Bacteroidetes* was decreased, while the relative abundance of *Muribaculaceae, Alistipes* and *Rikenellaceae*_RC9_group was increased after the administration of AFB compared with HFD-mice. These results demonstrated that AFB can prevent diet-induced obesity and provides a new option to modulate obesity-related gut dysbiosis.

Short chain fatty acids (SCFAS) containing butyrate from fermentation by endophytic bacteria in *Aloe vera* gel

Aloe vera extracts have antimicrobial and anti-fungal activities which may be able to treat minor skin infection. In spite of these antimicrobial activities the inner leaf gel containing acemannan (non-digestible polysaccharide), leads to fermentation with endophytic bacteria and resulted in SCFAs-production, containing butyric acid in gel fermentation [8]. Fermentation by endophytic bacteria in *Aloe vera* gel provided butyric acid, suggesting that the daily application of fermented *Aloe vera* gel may be beneficial to putative prophylaxis of butyric acid for health and QOL as an immune modulator.

Exercise and butyrate supplementation exert metabolic beneficial in both mice and human

Yu., *et al*. [9] examined the effect of exercise training and dietary supplementation of butyrate on the composition of gut microbiota and whether the altered gut microbiota can stimulate differential production of short chain fatty acid (SCFAs), which promote the expression of SESNS and CRTC2 to improve metabolic health and protect against obesity. C578L/6J mice were used to study the effect of exercise and high fat diet (HFD) with or without sodium butyrate (NaB) on gut microbiota. Exercise and butyrate administration significantly reversed metabolic dysfunctions induced by HFD. The number of *Firmicutes* and the proportion of *Firmicutes* to *Bacteroidetes* order were predominant in all HFD groups. Exercise and butyrate supplementation significantly inhibited the relative abundance of lipopolysaccharide-producing phyla. SESN2 and CRTC2 expression in the liver of mice were significantly increased after exercise and/or supplementation of butyrate. Exercise enhances butyrate-producing fecal bacteria and increases butyrate production and consequently improves lipid metabolism through the butyrate-SESN2/CRTC2 pathway. Excess butyrate may reduce the proportion of probiotics and reverse the metabolic effects.

Dietary fiber consumption associated with beneficial effects in including amelioration of obesity and insulin resistance

The polysaccharide in *Aloe vera* gel produces short chain fatty acids, including propionate, acetate and butyrate, during fermentation in the colon and with the endophytic bacteria. The beneficial effects of butyrate supplementation in peripheral tissue in the prevention and reversal of obesity and insulin resistance were focused in the previous review [10] and the possible efficacy of *Aloe vera* gel metabolites in long-term ingestion to insulin sensitivity [11]. In obese individuals with prediabetes or early untreated diabetes mellitus (n = 136), *Aloe vera* gel complex reduced body weight, body weight, body fat mass and insulin resistance at 4 and 8 weeks [12]. A possible beneficial efficacy of *Aloe vera* juice ingestion in long time may participate to obesity and prone to obesity subjects.

Slimming effect of ingesting a supplement that contains butyric acid bacteria

Hayashida., *et al*. [13] examined the slimming effect of ingesting of a health supplement; LAKUBI that contains butyric acid bacteria and exercise. The author recruited the female (20 - 39 years-old) who have higher body and mass index (BMI) for examination of LUAKUBI. Twenty to thirty-nine years-old female who have more than 23 BMI and healthy without food allergy were examined by application of LAKUBI. The study was conducted under the control of Japan Clinical Trial Association. The test schedule was January 24-April 20, 2018.

Test samplings: LAKUBI nutrients (one sample; 269 mg): energy 1.03 kg, protein 0.06g, fat 0.008g; carbohydrate 0.18g and salts, 0.00075g; LAKUBI with raw microbiota: *Salacia* extract, dextrin, *Bifidus bacterium*, butyrate-producing microbiota, etc.

Test group A: LAKUBI single use for 16 subjects; Group B: LAKUBI with raw microbiota use for 16 subjects, Group C: control group without LAKUBI and raw microbiota for 16 subjects.

Group A, B and C were examined under the standard food supply and exercise for 12-weeks.

Outcomes of the study are estimated on her hip and waistline, weight, body fat index and BMI.

Results: The examination of 38 female individuals showed that group A and B revealed significant ($P < 0.05$) decrease of hips and west line, body fat ratio after 6-weeks, and significant ($P < 0.01$) decrease of west line, body weight and BMI after 12-weeks. Safety of the test two group subjects were determined. Slimming effect of LAKUBI, containing butyric acid-producing bacteria, was shown without any side effects. The improvement of gut-circumstance with *Clostridium butyricum* and rice-bran-fermented 3-(4-Hydroxyphenyl) propionic acid was claimed as Foods with Functional Claims on 2022 [14].

Effect of cereal fibers on short chain fatty acids in healthy and patients: A meta-analysis of randomized clinical trials

Bai., *et al*. [15] reviewed relevant clinical studies between 1950 and 2021 and aimed to evaluate the effect of cereal fiber consumption on short chain fatty acids (SCFAs) production in healthy subjects and patients. PubMed, Web of Science, and the Cochrane Library

databases were used for systematically searching published relevant trials with adults and a minimum intervention duration of 2 weeks. The results of meta-analysis revealed that cereal fiber supplementation significantly increased acetate, propionate, butyrate and SCFAs concentration. Subgroup analysis suggested that a long intervention duration (> 4 weeks) significantly promoted acetate and propionate production, whereas a short intervention duration (≤ 4 weeks) significantly facilitated butyrate production. Cereal fiber supplementation had a more significant impact on overweight and obese subjects with body mass index (BMI) > 29 kg m^{-2} than on individuals with BMI ≤ 29 kg m^{-2}. Furthermore, the author found that cereal fibers and wheat/rye arabinoxylan oligosaccharides, rather than wheat bran fibers, barley fibers, and barley ß-glucan, could significantly elevated the SCFAs concentration. The results of meta-analysis demonstrated that cereal fiber supplementation is helpful in increasing the SCFAs concentration, which provided strong proof for the beneficial role of cereal fibers.

What is the prevalence of obesity in pediatric patients with type 2 diabetes?

Cioana., *et al*. [16] evaluated the global prevalence of obesity in pediatric Type 2 diabetes (T2D), examined the association of sex and race with obesity risk, and assessed the association of obesity with glycemic control and dyslipidemia. The author searched NEDLINE, Embase, Cochrane Library, and Web of Science as Data sources from database inception to June 16, 2022. Selected observational studies with at least 10 participants reporting the prevalence of obesity in patients with pediatric T2D were included. Of 57 articles included in the systematic review, 53 articles, with 8942 participants were included in the meta-analysis. The overall prevalence of obesity among pediatric patients with T2D was 75.27%, and the prevalence of obesity at diabetes diagnosis among 4688 participants was 77.24%. While mate participants had higher odds of obesity than female participants. Asian participants had the lowest prevalence of obesity, and White participants had the highest prevalence of obesity compared with other racial groups. Higher heterogeneity across studies and varying degrees of glycemic control and dyslipidemia were noted. In conclusion, the finding of the systematic review and meta-analysis suggested that obesity is not a universal phenotype in children with T2D.

Therapeutic effects of butyrate on pediatric obesity: A randomized clinical trial

Coppola., *et al*. [17] investigated whether oral butyrate supplementation as an adjunct to standard care is effective in the treatment of pediatric obesity. A randomized, quadruple-blind, placebo-controlled trial was performed from November 1, 2020 to December 31, 2021, at the Tertiary center for Pediatric Nutrition, Department of Translational Medical Science, University Naples Federico II, Naples, Italy. Participant (N = 54) of included children aged 5 to 17 years with body mass index (BMI) was greater than the 95 percent. Standard care for pediatric obesity supplemented with oral sodium butyrate, 20 mg/kg body weight per day, or placebo was administrated for 6 months.

The main outcome was the decreases of at least 0.25 BMI SD scores at 6 months. The secondary outcomes were changes in waist circumference; fasting glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, triglyceride, ghrelin, microRNA-221, and interleukin-6 levels; homeostatic model assessment of insulin resistance (HOMA-IR), dietary and lifestyle habits; and gut microbiome structure. At intention-to-treat analysis (N = 54), children treated with butyrate had a higher rate of BMI decrease greater than or equal to 0.25 SD scores at 6 months.

The study suggested that in children with obesity, oral butyrate supplementation may produce a reduction of BMI and exerts beneficial effects on glucose metabolism and inflammation. These data support the importance of the gut microbiota-derived metabolite butyrate as a protective factor against pediatric obesity, highlighting the central role of a healthy diet and gut microbiota function to achieve an optimal endogenous production of butyrate as an adjuvant. Butyrate, a known histone deacetylase inhibitor that stimulates expression of numerous genes involved in immune system pathways, was studied extensively for its adjuvanticity and effects on virus infection [18].

Butyrate supplementation affected the trained immunity in monocytes of obese individuals with metabolic complications

Cleophas., *et al*. [19] studied the systemic anti-inflammatory effects induced by sodium butyrate (SB) supplementation in humans. Nine healthy (Lean) and ten obese (metabolic syndrome group, MetSyn) males were given 4 grams SB daily for 4 weeks. Peripheral blood

mono-clear cells were isolated before and after supplementation for direct stimulation experiments and induction of trained immunity by oxidized low-density lipoprotein, ß-glucan, or Bacillus Calmette Guerin vaccine (BCCG). SB supplementation moderately affected some of the cytokine responses in the MetSyn group. Induction of trained immunity by ß-glucan was decreased by SB in the MetSyn group for Pam3CSK4-induced IL-10 production. SB supplementation affected trained immunity in monocytes of obese individuals with metabolic complications. Therefore, the author expressed that oral butyrate supplementation may be beneficial in reducing the overall inflammatory status of circulating monocytes in patients with metabolic syndrome.

Effect of *Lactobacillus plantarum* LMT1-48 on body fat in overweight subjects

Sohn., *et al*. [20] investigated whether *Lactobacillus plantarum* LMT1-48, isolated from Korean fermented foods, such as kimchi, and newborn feces, is a suitable probiotic supplement to treat overweight subjects. In this randomized, double-blind, placebo-controlled clinical trial, 100 volunteers with a body mass index of 25 to 30 kg/m^{-2} were assigned randomly (1:1) to receive $2x10^{10}$ colony forming units of LMT1-48 or to a placebo treatment group. Changes in body fat, visceral fat (VFA) anthropometric, and biomarkers were compared between the two treatment groups. After 12 weeks of treatment, the decrease in body weight and body mass index by treatment with LMT1-48 was correlated with increase in Lactobacillus levels significantly. LMT1-48 also increased *Oscillibacter* levels significantly, which were negatively correlated with triglyceride and alanine transaminase levels. In conclusion, administration of LMT1-48 decreased body weight, abdominal VFA, insulin resistance, and leptin levels in these subjects with overweight, suggesting its anti-obesogenic potential. The present randomized clinical trial (NCT03759743) demonstrated the therapeutic potential of LMT1-48 in treating human obesity. The data regarding the gut microbiota are largely in agreement with other studies showing that the gut microbiota play key roles in human energy metabolism and the pathogenesis of obesity.

Dietary OTC-prebiotics could help children and adolescent with obesity producing more short chain fatty acids (SCFAs)

Holmes., *et al*. [21] used an *in vitro* system to examine the SCFAs production by fecal microbiota from 17 children with obesity (age, 10 to 18 years old) when exposed to five different commercially available over-the counter (OTC) prebiotic supplements. OTC prebiotic supplements; dextrin, inulin, fructo-oligosaccharide, xylo-oligosaccharide and galacto-oligosaccharide may be unequal in their ability to stimulate SCFAs production in children and adolescent with obesity and that the most acidogenic may differ across individuals. The author suggested that prebiotic supplements could help children and adolescents with obesity, but that these therapies may not be one size fits all.

Case reports: Children-growth supported with *Aloe vera* juice ingestion

Case report 1: A 9-years-old female born in April 2013, who had 130 cm height, 42 kg body weight and Rhorer index ($w/h^3 \times 10^4$) 186.6, suffered from atopic dermatitis.

She started to drink *Aloe vera* juice (AVJ) 50 ml/d on Apr. 2013, and had 136 cm height, body weight 35 kg and Rhorer index 139.1 on Oct. 2013. She continued to drink AVJ 50 ml/d and had no constipation, no atopic dermatitis, and got a high amount of exercise. She, 23-years old, had 159 cm height, body-weight 50 - 54 kg and no atopic dermatitis, with AVJ drinking 100 ml/d, and was well-being on December 2022. In our case reports of atopic dermatitis, the risk-remission for steroid-induced atopic dermatitis in male student at 20-years and 30-years male by using of AVJ ingestion had been expressed [22].

Case report 2: A 12-years-old female born in June 2010, who had 152 cm height, 60 kg body weight and Rhorer index 170.8, had grown over fat. After then, she became a non-attender student on June, 2015. Since then, she started to drink AVJ every 100 ml/d. Her body weight decreased 54.5 kg, Rhorer index 138.1 and her height became 158.9 cm. She started her first menstrual period and had a well-being QOL. In 23-years-old she continued to drink AVJ 100 ml/d with her exercise. and kept her height 160 cm and her body weight 50 - 52 kg with her well-being on December 2022.

Summary

Present review is focused on butyrate fermented in *Aloe vera* gel to obesity-prone and pediatric subjects. Body mass, BMI or Rhorer index is central to the development and rising incidences of obesity subjects. A possible benefit of butyrate fermented in *Aloe vera* gel in long time digestion may participate to obesity-prone children, supporting the relationship between the conditions of the obese individuals and the development of metabolic alterations. In case reports we expressed the children-growth strongly supported with *Aloe vera* juice daily ingestion. An obesity often leads to all kinds of disease and is a root cause of many diseases in children growth specially.

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