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EDITORIAL

Gut Microbiota: Influence of *Aloe vera* gel and Calorie Restriction

Akira Yagi, Byung Pal Yu

Akira Yagi, Editor In-Chief of J. of GHR, PhD, Emeritus Professor, Fukuyama University, Hiroshima, Japan
Byung Pal Yu, PhD, Professor Emeritus, University of Texas, Health Science Center. Department of Physiology, San Antonio, Tx, the United States

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Correspondence to: Akira Yagi, PhD, Emeritus Professor, Kasuya-machi, Kasuya-gun, Fukuoka-ken, 811-2310, Japan.
Email: akirayagi@nexyzbb.ne.jp
Telephone: +81-92-938-2717
Fax: +81-92-938-2717

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ABSTRACT

The health-promoting potential of a balanced gut microbiota status modulated by calorie restriction (CR) posits a possible close link between gut microbiota (GM) and healthy aging. Short chain fatty acids (SCFAs) generated from intestinal bacterial fermentation may act as mediators between the microbiota and the immune system. In this review, a putative prophylactic role of butyric acid from endophytic bacteria fermentation of *Aloe vera* gel was described to suggest that the consumption of fermented extract of *Aloe vera* gel may be beneficial for health and QOL as an immune modulator.

Key words: *Aloe vera* gel; Butyrate; Obesity; Calorie restriction

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INTRODUCTION

Dietary metabolism and immuno-modulatory activity are inextricably linked, allowing organisms to adapt to diverse changes in their intestinal gut environment. It has been shown that insulin sensitivity can be modulated by metabolites of *Aloe vera* polysaccharide, such as a manno-oligosaccharide and SCFAs[1]. The SCFAs are bacterial fermentation products formed in high concentrations in the intestine, and these metabolites modify microbiota status and immune system. Intestinal epithelial cells take up SCFAs through passive and active mechanisms. Once inside the cells, they are partially used as a source of energy, but mainly for the production of immune mediators.

The health-promoting potential of a balanced GM status induced by CR reveals a possible close interaction between GM and healthy aging. For the consideration of health maintenance with *Aloe vera* gel in long-term ingestion by the intestinal microbiota during aging, our present review describes effects of *Aloe vera* gel on immune modulation, GM status, CR and role of SCFAs including butyric acid.

ALOE VERA GEL ON IMMUNE MODULATION

Longevity is modulated by the biological aging process and the age-related disease process which are influenced by both genetical and various environmental factors. Recent evidences clearly indicate that the latter factors, including GM and CR play predominant roles. It has been shown that *Aloe vera* supplement in larval diet delayed the aging process of fruit fly, *Drosophila melanogaster*. Their longevity seems to be effected by multi-factorial mechanisms involving efficient lipid utilization, prevention of neuro-degeneration, regeneration of nerve fibers and upregulation of anti-oxidative defensive enzymes[2]. Alterations in the composition of the intestinal microbiota have been correlated with aging in flies. The bacteria of *D.melanogaster* of different stages was qualified

by 454 pyrosequencing of 16S RNA gene amplicons, and assigned to *Acetobacter pomorum*, *A.tropicalis*, *Lactobacillus brevis*, *L.fructivorans* and *L.plantarum*. A developmental change in the most abundant species, from *L.fructivorans* in young adults to *A.pomorum* in aged adults was identified. Host immune responses and disturbance may contribute to the low bacterial diversity in the *Drosophila* gut habitat[3]. Dysbiosis of the intestinal microbiota, characterized by an expansion of the *Gammaproteobacteria* (class), *Acetobacteria* (family), is tightly linked to age-onset intestinal barrier dysfunction in *Drosophila*. Clark group indicated that a distinct shift in microbiota composition follows intestinal barrier dysfunction, leading to systemic immune activation and organismal death. Alterations in microbiota dynamics could contribute to and also predict varying rates of health decline during aging in mammals[4]. The pro-longevous effect of a life-long ingestion of *Aloe vera* suppressed the occurrence and severity of age-related diseases by attenuating the age-associated physiological decline in male Fischer 344 rats[5]. *Aloe vera* gel high molecular fraction exhibited immunomodulating responses as carbohydrate-based adjuvants, and the possible efficacy for insulin sensitivity in long-term ingestion[1]. A life-long ingestion of *Aloe vera* gel produced a strong anti-oxidative action against free radical-induced oxidation damage and lipid peroxidation of male specific pathogen-free Fischer 344 rats, as indicated by reduced levels of hepatic phosphatidylcholine hydroperoxide. In the same study, it was shown that age-related increase in hepatic cholesterol in the control group, was markedly reduced (approximately 30%) by the aloe digestion, thereby showing a hypocholestremic efficacy[6]. More interestingly, the beneficial metabolic effects of an *Aloe vera* gel complex (ie. *Aloe vera* gel + aloesin) were recently reported: Choi *et al*, measured randomized controlled obese patients with prediabetes or early diabetes mellitus (DM) for body weight, body fat mass (BFM), fasting blood glucose, fasting serum insulin, and homeostasis model of assessment-insulin resistance. The results showed in these individuals with prediabetes or early untreated DM, *Aloe vera* gel complex reduced body weight, BFM, and insulin resistance[7].

GM MODULATION AND CR

The precise molecular mechanisms underlying the interaction between obesity and insulin resistance have not determined despite they have been under intensive scrutiny in recent years because of their prevalence and seriousness as the current major health issues. Nutrient related adverse consequences for health and potentially aging are shown to be related to our unhealthy life-style including a high-sugar or high-fat diet, excessive alcohol consumption, cigarette smoking and a lack of exercise.

CR without malnutrition is the most powerful intervention to increase lifespan in simple model organisms and rodents. CR decreases inflammation, which is believed to protect against age-related diseases.The RCT study by Meydani group showed that moderate long-term CR without malnutrition decreases inflammation in non-obese, healthy adults, as demonstrated by reduced number of WBC, lymphocytes, and neutrophils in blood, as well as reduced circulating levels of CRP, leptin, TNF-α, and ICAM-1, with no significant adverse effect on key in vivo indicators of cell-mediated immunity.These CR-induced changes suggest a shift toward a healthy phenotype, given the established role of these pro-inflammatory molecules as risk markers in the development of metabolic syndrome and age-related chronic disease, in particular cardiovascular disease, type 2 diabetes, and cancer[8].

It has been well documented that unhealthy diet especially the fast foods, untraditional foods or bad eating habits influence our GM status that modifies immune responses, thus affecting our metabolomic profiles during lifetime. Furthermore, many studies highlight the molecular pathways that mediate host and symbiotic interactions that regulate proper immune function and the putative action against cancer. It is important to realize that the cancer incidence increases due to the weaken immune system through deteriorated microbiotic competence. Therefore, as a preventive measure, it would be beneficial to suppress cancer progenitors, like cancer stem cells by GM-restoring CR before tumor development. This notion was highlighted by Eslami *et al*, who suggested the early CR with annual fasting practice on the cancer prevention by enhancement of immune system through the healthy GM[9].

CR, a reduced intake of balanced meal without malnutrition is regarded as the only effective experimental paradigm that can slow aging and retard the onset of age-related diseases, and a hallmark of the anti-aging intervention, it extends substantially the lifespan of most of the experimental organisms tested, including non-human primates, although the actual mechanism remains unresolved. As mentioned earlier, GM that plays a pivotal role in maintenance of host health, which is heavily modulated by dietary conditions. Zhang *et al*, showed that life-long CR on both high-fat or low-fat diet, but not voluntary exercise, significantly changes the overall structure of the GM of C57BL/6 J mice. CR enrichs phylotypes positively correlated with lifespan, for example, the genus *Lactobacillus* on low-fat diet, and reduces phylotypes negatively correlated with lifespan. These CR-induced changes in GM occurred concomitantly with significantly reduced serum levels of lipopolysaccharide-binding protein, suggesting that animals under CR can establish a structurally balanced GM environment, likely leading to exert a health benefit to the host via reduction of antigen load from the gut[10].

It has been suggested that CR with balanced diet may promote the healthy microbiota, leading to longevity by down-regulating the adverse inflammatory process. Dysbiosis, a microbial imbalance or maladaptation on or inside the body, such as an impaired microbiota, leads to body dysfunction, including metabolic disorders, that cause poor epithelial architecture, and impeding the development of mucosal-associated lymphoid tissue. These alterations eventually result in reduced T and B cell populations, rendering the body prone to infections, allergy and possibly cancer as some GM enzymes are a risk factor for cancer while gut-derived interleukin-6 is associated with hepatocellular carcinoma development. GM can also influence the brain biochemistry and emotional behavior. The altered GM affects the genes involved in second messenger pathway and long-term potentiation, leading to their differential expression in the hippocampus, cortex, striatum and cerebellum. In addition, the dysbiotic GM is associated with autistic disorder. Khan *et al*, reported that living with dysbiotic GM is unhealthy and risky with consequences of serious impairments[11]. Genton *et al*, reviewed the present knowledge regarding the in vivo impact of depleted nutritional states on structure and function of the GM in addition to the gut epithelium, the gut-associated lymphoid tissue, and the enteric nervous system. Their article revealed the complexity of the interactions between the components of gut barrier in depleted states due to food restriction and protein energy wasting and shows that these interactions are multi-directional nature to suggest the existence of feedbacks pathway[12].

One of the interesting aspect of GM is that its status in obese subjects is different from that of lean subjects, implying the possibility of its involvement in the maintenance of the body metabolism such as energy utilization and fat metabolism. A recent

revelation on a bacterium's action on fat mass is interesting. For example, *Akkermansia muciniphila*, a mucin-degrading bacterium, has been inversely associated with body fat mass and glucose intolerance in mice. For human subjects with overweight and obese adults (n = 49, including 41 women), Dao MC, *et al*, looked into the association between fecal *A.muciniphila* abundance, fecal microbiome gene, diet, host characteristics, and their changes following CR. This CR intervention consisted of a 6-week CR period followed by a 6-week weight stabilization diet. Fecal *A.muciniphila* abundance, fecal microbial gene richness, diet and bioclinical parameters were measured at baseline and after CR. Individuals with higher baseline *A.muciniphila* displayed greater improvement in insulin sensitivity and other clinical parameters after CR. These participants also experienced a reduction in *A.muciniphila* abundance, but it remained significantly higher than in individuals with lower baseline abundance. *A.muciniphila* was associated with microbial species known to related to health. *A.muciniphila* is associated with a healthier metabolic status and better clinical outcomes after CR by overweight/obese adults. This trial is registered with clinical trial registration number NCT01314690. Official title: Human intestinal microbiota in obesity and nutritional transition (Micro-obes)[13].

To explore the effects of long-term dietary interventions on metabolic perturbations, Wu *et al*, investigated serum and urinary metabolic changes induced by interactive high/low fat diet in combination with/without reduced caloric intake over a life span in mice using NMR-based metabonomics. The authors found that the calorie intake index exerts a dominant effect on metabolic perturbations irrespective of the dietary composition. Thus, this investigation provides a holistic view of the metabolic impact of long-term dietary interventions, which are important for detecting physiological changes and dietary effects on mammalian metabolism[14].

GM AND ROLE OF SHORT CHAIN FATTY ACIDS INCLUDING BUTYRIC ACID

Laparoscopic sleeve gastrectomy (LSG), a surgical intervention for obesity, is classified as predominantly restrictive procedure. Damms-Machado's team investigated functional weight loss mechaisms with regard to gut microbial change and energy harvest induced by LSG and a very low caloric diet in ten obese subjects (n = 5 per group) who demonstrated identical weight loss during a follow-up period of six months. For gut microbiome analysis next generation sequencing was performed and feces were analysed for targeted metabolomics. The energy-reabsorbing potential of the gut microbiota decreased following LSG, indicated by the *Bacteroidetes/Firmicutes* ratio, but increased during dieting. It was found that changes in butyrate-producing bacterial species were responsible for the *Firmicutes* changes in both groups. Although no alteration of fecal butyrate was observed, but the microbial capacity for butyrate fermentation decreased following LSG and increased following dietetic intervention. LSG resulted in enhanced fecal excretion of nonesterified fatty acids and bile acids. LSG, but not dietetic restriction, improved the obesity-associated gut microbiota composition towards a lean microbiome phenotype. Moreover, LSG increased malabsorption due to loss in energy-rich fecal substrates and impairment of bile acid circulation. This trial is registered with clinical Trial.gov NCT01344525. Official title: Pilot project on interdisciplinary therapy of obesity[15].

Obesity has been linked to not only to the composition of human microbiota, but also to the production of SCFAs. Schwiertz *et al*, evaluated the differences within the human intestinal microbiota and fecal SCFAs concentration of lean and obese subjects. A total of 98 subjects volunteered to take part in this study. The BMI in kg/m^2 of 30 volunteers was within the lean range, 35 were overweight and 33 were obese. The fecal microbiota was characterized by real-time PCR analyses. The total amount of SCFAs was 20% higher in obese subject group (p = 0.024) as compared to the lean subject group. The proportion of individual SCFAs changed in favor of propionate in overweight (p = 0.019) and obese subject (p = 0.028). The most abundant bacterial species in feces of lean and obese subjects belonged to the phyla *Firmicutes* and *Bacteroidetes*. The ratio of *Firmicutes* to *Bacteroidetes* changed in favor of the *Bacteroidetes* in overweight (p = 0.001) and obese subjects (p = 0.005). The results suggested that SCFAs metabolism might play a considerable role in obesity, but contradicted previous reports with regard to the contribution of various bacterial groups to the development of obesity[16]. SCFAs are found in high concentrations in the intestinal tract, from where they are taken up by intestinal epithelial cells (IECs), and partially utilized as a source of ATP by these cells. In addition, these fatty acids may act as mediators between the microbiota and the immune system by modulating different aspects of IECs and leukocytes development, survival and function through activation of G protein coupled receptors (FFAR2, FFAR3, GPR109a and Olfr78) and by modulation of the activity of enzymes and transcription factors including the histone acetyltransferase and deacetylase and the hypoxia-inducible factors. These molecule and their targets are suggested to have an important role in the maintenance of intestinal homeostasis and any changes in components of this system are associated with pathological conditions including inflammatory bowel disease, obesity and others. Correa-Oliveria *et al*, reported clear and updated description of the effects of SCFAs derived from bacteria on host immune system, as well as the molecular mechanisms[17].

Recent data concerning butyrate production delivery as well as absorption by the colonocytes are reported by Guilloteau's group. Butyrate cannot be detected in the periferal blood, which indicates fast metabolism in the gut wall and/or in the liver. Under physiological conditions, the increase in performance in animals could be explained by the increased nutrient digestibility, the stimulation of the digestive enzyme secretions, a modification of intestinal luminal microbiota and an improvement of the epithelial integrity and defence systems. It is also recorded that in the digestive tract, butyrate can act directly (upper gastrointestinal tract or hind-gut) or indirectly (small intestine) on tissue development and repair. Direct trophic effects have been demonstrated mainly by cell proliferation studies, to indicate a faster renewal of necrotic areas. Indirect actions of butyrate are believed to involve the hormono-neuro-immuno system. Butyrate has also been implicated in down-regulation of bacteria virulence, both by direct effects on virulent gene expression and by acting on cell proliferation of the host cells. For animal production, butyrate is a helpful feed additive, particularly when ingested soon after birth, as it enhances performance and controls gut health disorders caused by bacterial pathogens. Such effects could be considered for new applications in human nutrition[18].

Relationship between the development of human colorectal cancer (CRC) and the composition of GM in CRC was shown by Wang's group[19]. Fecal bacterial diversity in CRC patients (n = 46) and healthy volunteers (n = 56) were profiled by 454 pyrosequencing of the V3 region of the 16S ribosomal RNA gene. Both principal component analysis and UniFrac analysis showed structural segregation between the two populations. Forty-eight

operational taxonomic unites (OTUs) were identified by redundancy analysis as key variables significantly associated with the structural difference. One OTU closely related to *Bacteroides fragilis* was enriched in the GM of CRC patients, whereas three OTUs related to *Bacteroides vulgatus* and *Bacteroides uniformis* were enriched in that of healthy volunteers. A total of 11 OTUs belonging to the genera *Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus* and *Peptostreptococcus* were significantly more abundant in the GM of CRC patients, and 5 OTUs belonging to the genus *Roseburia* and other butyrate-producing bacteria of the family *Lachnospiraceae* were less abundant. Real-time quantitative PCR further validated the significant reduction of butyrate-producing bacteria in the gut microbiota of CRC patients as revealed by measuring the copy numbers of butyryl-coenzyme A CoA transferase genes (Mann-Whitney test, $p < 0.01$). Reduction of butyrate producers and increase of opportunistic pathogens may constitute a major structural imbalance of GM in CRC patients.

The life of intestinal epithelial cells (IECs) is short (3-5 days), its regulation is thought to be important for homeostasis of the intestinal epithelium. The investigation on the role of commensal bacteria in regulation of IEC turnover in the small intestine was demonstrated by Park *et al*[20]. The proliferative activity of IECs in intestinal crypts as well as the migration of these cells along the crypt-villus axis were markedly attenuated both in germ-free mice and in specific pathogen-free (SPF) mice treated with a mixture of antibiotics, with antibiotics selective for Gram-positive bacteria being most effective in this regard. Oral administration of chloroform-treated feces of SPF mice to gem-free mice resulted in a marked increase in IECs turnover, suggesting that spore-forming Gram-positive bacteria contribute to this effect. Oral administration of SCFAs as bacterial fermentation products also restored the turnover of IECs in antibiotic-treated SPF mice as well as promoted the development of intestinal organoids in vitro. Antibiotic treatment reduced the phosphorylation levels of ERK, ribosomal protein S6, and STAT3 in IECs of SPF mice. The results suggested that Gram-positive commensal bacteria are a major determinant of IEC turnover, and that their stimulatory effect is mediated by SCFAs.

There is a growing interest in butyrate because its role in the epigenetic modifications as a potent histone deacetylase inhibitor that will lead to more specific and efficacious therapeutic strategies for the treatment of different disease raging from genetic/metabolic conditions to neurological degeneration disorders. The dietary natural source of butyrate through a high fiber diet or butyrate produced by fermentation of non-digestive fiber, such as acemannan in *Aloe vera* gel, is highly appealing approach to present a simple and selectively lower risk method to potentiate the improved outcomes in aged people with brain dysfunctions. Recently, Yagi *et al*[21] discussed the potential pharmacological effect of butyrate as a histone deacetylase inhibitor on insulin resistance and energy expenditure, and as pro-drugs for ulcerative colitis and cancer, and the gut-liver axis in pre-clinical treatment.

SUMMARY AND CONCLUSION

In the present article, the role of GM was discussed in terms of host-microbiota interactions modulating host metabolism. The mechanism of weight loss via altered host-microbial interactions of popular bariatric procedures, Roux-en-Y gastric bypass and sleeve gastrectomy is still elusive and appears to be complex. Potential mechanisms of diabetes remission after bariatric surgery were reviewed by Cho[22]. One of the changes was alteration in GM composition and population. The production of SCFAs by GM, *Akkermansia muciniphila* (mucin-degrading bacteria linked with a fiber-rich diet, associated with lower levels of blood sugar, insulin and fats which help ward off obesity, diabetes and heart disease.), which is associated with a healthier metabolic status and better clinical outcomes after calorie restriction in overweight/obese adults, may play an important role. *A.muciniphila* produces a variety of fermentation products including SCFAs, through mucin degradation. These substrates may serve as energy sources for other bacteria and the host. *A.muciniphila* may be identified as a diagnostic or prognostic tool to predict the potential success of dietary interventions[13]. *A.muciniphila* abundance has been shown to inversely correlate with obesity and associated metabolic disorders. The athletes from an international rugby union squad, in the low body mass index (BMI) group had significantly higher proportions of *A.muciniphila* levels compared with the higher BMI group. Clarke group provided evidence for a beneficial impact of exercise on GM diversity and indicated that exercise is another important factor in the relationship between the GM, host immunity and host metabolism, with diet playing an important role[23]. Alterations in intestinal microbiota are associated with obesity and insulin resistance.

Vrieze group reported the effects of infusing intestinal microbiota from lean donors to male recipients with metabolic syndrome on the recipient's microbiota composition and glucose metabolism. Six weeks after infusion of microbiota from lean donors, insulin sensitivity of recipients increased along with levels of butyrate-producing intestinal microbiota. The data suggest that fecal transplant from lean donors to metabolically unhealthy people improved insulin sensitivity and increased populations of butyrate-producing gut microbiota. Butyrate is produced by microbiota both in the large and small intestines for energy and signaling purposes, with orally administrated butyrate having a direct effect on glucose metabolism. The increased gut microbiota diversity also is associated with improved insulin resistance[24]. Obesity has been considered as a primary source of metabolic dysfunction instigated by inflammatory insulin resistance. Accumulating evidence indicates that the gut microbiota plays a significant role in the development of obesity, obesity-associated inflammation and insulin resistance.

The up-to-date descriptions of gut microbiota and role of SCFAs suggest that daily intake of the butyric acid fermentation extract from *Aloe vera* inner gel with endophytic bacteria, may provide the possible potential preventive and therapeutic roles in human health[25]. Intestinal microbiota producing butyrate might be developed for the therapeutic purpose to increase insulin sensitivity in humans with CR. Based on what is known about the unique function of GM, it should now be considered a potent hidden metabolic organ of the human body to provide metabolically essential biochemical functions that needed for the maintenance of the healthy physical integrity.

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