

Putative Roles of Butyrate Fermented in Aloe Vera Gel For Depression: Case Reports of Meniere's Disease and Acute Vestibular Deficit

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ABSTRACT

Host microbial cross talk is essential to maintain intestinal homeostasis. Long term successive ingestion of aloe vera juice (AVJ) for brain and behavior may help to modulate the immune-sensitivity via pathogenesis and homeostasis, and provide high concentration of microbiome in the host gut. In case reports 1-4, we reported the improvement of Meniere's disease (MD), paradoxical healing response, a sudden deafness and cerebrovascular disorder with the preparation of MD medicine and Kampo product with daily digestion of AVJ as an adjuvant.

Key words: Aloe vera gel; Fermented butyrate; Suppression; Meniere's disease; Acute vestibular deficit

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INTRODUCTION

There are many psychological factors contributing to accelerating the progression of type 2 diabetes. Daily depression is the most important psychological factor involved in diabetic development.

Aloe vera has anti-diabetic, anti-oxidative, and neuroprotective effects. The effects of *Aloe vera* gel on behavioral functions, oxidative status, and neuronal viability in the hippocampus of streptozotocin-induced diabetic rats was determined by Tabatabaei et al^[1]. The results suggested that both interrelated hypoglycemic and anti-oxidative properties of *Aloe vera* gel are possible mechanism that improve behavioral deficits and protect hippocampal neurons in diabetic rats. Foadoddini et al^[2] investigated the effects of *Aloe vera* gel powders on depression in pre-diabetic patients. After the 8-weeks of intervention, the mean depression score in the *Aloe vera* gel 500mg (AL500) group was significantly decreased, concluding that *Aloe vera* gel powder (AL500) group could considerably reduce depression mean scores in pre-diabetic patients after 8-weeks of treatment. (Ilanian registry of clinical trials: IRCT2013041112984N1) Depression is one of the major mood disorders leading to the development of type2 diabetes in pre-diabetic patients and any intervention that can reduce the symptoms of depression in pre-diabetes patients will have a significant impact on preventing type2 diabetes. The comorbidity of depression and diabetes can be seen as a prototypical example of mental/physical comorbidity. The prevalence of both conditions is growing, and depression is twice as frequent in people with diabetes compared with these without diabetes. The comorbidity of mental and physical disorders is a major challenge for health care worldwide. Sartorius^[3] reviewed the epidemiology

and risk factors of the comorbidity of depression and diabetes. Suksomboon *et al*^[4] undertook a systematic review and meta-analysis to assess the effect of *Aloe vera* on glycemic control in pre-diabetes and type 2-diabetes. The author performed systematic review and meta-analysis to the end of January 2016 to evaluate the effect of *Aloe vera* on glycemic control in pre-diabetes and type2 diabetes to establish its therapeutic benefit in these patients.

Major depression disorders (MDD) is a complex, multifactorial and heterogeneous clinical syndrome that currently affects at least 120 million people worldwide. MDD is a global problem for which current pharmacotherapies are not completely effective. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has long been associated with MDD; however, the value of assessing cortisol as a biological benchmark of the pathophysiology or treatment of MDD is still debated. Nandam *et al*^[5] evaluated the relationship between HPA axis dysfunction and cortisol level in relation to MDD subtype, stress, gender and treatment regime, as well as in rodent models. The author found that elevated cortisol response to stress is associated with acute and severe, but not mild or atypical, forms of MDD. The increased incidence of MDD in females is associated with greater cortisol response variability rather than higher baseline levels of cortisol. In both mouse and humans, stress leads to secretion of corticotropin releasing hormone (CRH) and arginine vasopressin from the hypothalamus, which subsequently stimulates the secretion of adrenocorticotropic hormones (ACTH) from the pituitary gland. ACTH transported via blood to the adrenal cortex of the adrenal gland stimulates the synthesis and secretion of glucocorticoid; primarily corticosterone, in mice and cortisol in humans as well as secretion of other major steroid dehydroepiandrosterone. In MDD, glucocorticoid receptor signaling is abnormal and associated with chronic hypersecretion from the CRH neurons of the HPA axis. The hypersecretion is thought to shift HPA activity toward ever higher set points, resulting in the persistently elevated HPA activity seen in some MDD patients. The evidence supported the notion that cortisol dysfunction is proportionate to, and consistent with, current nosological classifications of MDD severity. The association of HPA dysregulation with MDD severity might be mechanically explained by parallel findings from receptor, immunological, and imaging studies.

Short chain fatty acids (SCFAs) are products of microbial fermentation of dietary fiber in the colon and may mediate microbiota-gut-brain communication. In our previous paper *Aloe vera* inner leaf gel containing acemannan: non-digestible polysaccharide, leads to fermentation with endophytic bacteria and results in bacterial growth promotion. Butyric acid was identified by GC/MSD analysis^[6], and the endophytic microbiota was identified as follows: *Bacillus cereus*, *B. licheniformis*, *Lactobacillus paralimentarium*, Yeast: *Clavispora lusitaniae*^[7]. The role of SCFAs in modulating psychological processes that underlie the development of stress- and anxiety-related disorders is not mechanically studied in humans. In the triple-blind, randomized, placebo-controlled intervention trial, Dalile *et al*^[8] examined in a parallel group design the effects of 1-week colonic SCFAs- mixture delivery in doses equivalent to fermentation of 10g or 20g of arabinoxylan oligosaccharides on responses to psychosocial stresses and fear tasks in 66 healthy men. The author found that low and high doses of SCFAs significantly attenuated the cortisol response to psychosocial stress compared to placebo. Both doses of SCFAs increased serum SCFAs levels and this increase in circulating SCFAs covaries significantly with the attenuation of the cortisol response to psychosocial stress. The results demonstrated that colon-delivered SCFAs modulate hypothalamic-pituitary- adrenal axis reactivity to psychosocial

stress, thereby supporting their hypothesized role in microbiota-gut-brain communication. The effect of *Lactobacillus plantarum* 299v on the salivary cortisol and salivary IgA levels in young adult under examination stress was investigated by Anderson *et al*^[9]. Forty-one students with an upcoming academic exam were included in a randomized double-blind, placebo-controlled study. A significant difference in cortisol levels was found between the treatment group and the placebo group, together with a significant increase in level of *L. plantarum* 299v in the treatment group compared with the placebo group. In conclusion, a probiotic bacterium with ability to reduce symptoms of irritable bowel syndrome prohibited increased levels of the stress marker cortisol during the examination period. The registration number of the study: NCT02974894.

In our previous paper, we demonstrated possible efficacy of *Aloe vera* gel metabolites in long-term ingestion to insulin sensitivity^[10] and possible hypoglycemic effect of *A. vera* gel high molecular weight fractions on type2 diabetes patients^[11]. In the present paper, we describe putative roles of butyrate fermented in *Aloe vera* gel to depression and comorbid brain disorders associated with pre-diabetic patients. In case reports, we describe that the successive aloe vera juice ingestion with Meniere's disease (MD)-medicine and Kampo product may possibly mitigates MD, migraine, tinnitus and paradoxical healing response.

PATHOGENESIS OF METABOLIC SYNDROME CLOSELY RELATED TO GUT MICROBIOME AND HOMEOSTASIS

Obesity is a chronic metabolic disease with an imbalance between energy intake and energy expenditure, and obesity-related metabolic diseases have become increasingly common. A growing number of symbiotic bacteria used as vectors for genetic engineering have been applied to create living therapeutics. Using *Bacillus subtilis* as a cellular chassis, Wang *et al*^[12] constructed the engineered butyrate-producing strain BsS-RS06551 with a butyrate yield of 1.5g/liter. A mouse model of obesity induced by a high-fat diet was established to study the long-term intervention effects of the butyrate-produced bacteria on obesity. The engineered butyrate-producing bacteria had potential as an effective strategy to prevent obesity in mice.

THE EFFECTS OF ENDOPHYTIC MICROBIOTA IN ALOE VERA GEL TO BUTYRIC ACID PRODUCTION AND ON GROWTH PERFORMANCE

Hydrogen and volatile fatty acid production by *Bacillus cereus* from sugarcane vinnasse

Vinnasse is a main residue of ethanol production, generated daily in large scale in Brazil. The anabolic processing of vinnasse can be a sustainable alternative for generation of fuel and co-products. The production of hydrogen and volatile fatty acids, such as acetic, propionic and butyric acid, was evaluated by *Bacillus cereus*, *Enterococcus faecalis* and *Enterobacter aerogenes* singly, as co-cultures, in bio-augmentation and microbial consortium by Eder *et al*^[13]. *B. cereus* showed high potential for hydrogen and volatile fatty acids production from sugarcane vinnasse. Butyric acid was predominant in fermentation with *B. cereus* and *E. faecalis*. In our previous paper the endophytic microbiota in Aloe vera gel were identified as butyric acid-producing microbiota as follows: *B. cereus*, *B. licheniformis* and *Lactobacillus paralimentarium*^[7].

Effects of dietary supplementation with *Bacillus subtilis* or *B. licheniformis* on growth performance, immunity, SCFAs production, antioxidant capacity and cecal microflora in broilers

Xu *et al.*^[14] investigated the effects of dietary supplementation with *B. subtilis* or *B. licheniformis* on growth performance, immunity, antioxidant capacity, SCFAs production, and the cecal microflora in broiler chickens. The chickens supplemented with either *B. subtilis* or *B. licheniformis* had comparatively higher body weight and average daily gain, whereas no difference was observed in feed efficiency. Concentrations of serum IgA, IgY, and IgM, as well as anti-inflammatory IL-10 were significantly increased and pro-inflammatory IL-1 β and IL-6 were significantly decreased by *B. subtilis* or *B. licheniformis* supplementation. Microbial analysis showed that both *B. subtilis* and *B. licheniformis* supplementation could increase butyrate-producing bacteria. *B. licheniformis* was more effective than *B. subtilis* with the same supplemental amount.

TRANSFER OF INTESTINAL MICROBIOTA FROM LEAN DONORS TO MALE RECIPIENTS WITH METABOLIC SYNDROME

Alterations in intestinal microbiota are associated with obesity and insulin resistance. Vrieze *et al.*^[15] investigated the effects of infusing intestinal microbiota from donors to male recipients with metabolic syndrome on the recipients' 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. Intestinal microbiota might be developed as therapeutic agent to increase insulin sensitivity in humans: Dutch trial registered (NTR1776).

CIRCULATING BUTYRATE RELATED TO INSULIN SENSITIVITY IN HUMANS

The gut microbiota ferments indigestible carbohydrate (e.g. aloe vera gel) and major end-products therefore are short chain fatty acids (SCFAs), such as acetate, propionate and butyrate. Acetate, propionate and butyrate are present in the colon in a ratio of approximately 3:1:1, respectively. In cross-sectional study (160 participants, 64% male, BMI: 19.2-41.0kg/m², normal or impaired glucose metabolism), associations between SCFAs (fecal and fasting circulating) and circulating metabolites, substrate oxidation and insulin sensitivity (IS) were investigated by Muller *et al.*^[16]. The author showed that circulating rather than fecal SCFAs were associated with glucagon-like peptide concentrations, whole-body lipolysis and peripheral IS in humans. Therefore, circulating SCFAs are more directly linked to metabolic health, which indicates the need to measure circulating SCFAs in human prebiotic/probiotic intervention studies as a biomarker/mediator of effects on host metabolism.

NOVEL VIABLE APPROACHES TO PREVENT OR RELIEVE OBESITY-ASSOCIATED NEUROPATHIES

Obesity affects over 2 billion people worldwide and is accompanied by peripheral neuropathy (PN) and an associated poorer quality of life. The increase in obesity has been accompanied by a rise in the prevalence of peripheral neuropathy. Because there is no disease-modifying therapy, paradigm-shifting research on pain associated with obesity, metabolic syndrome, and type2 diabetes is urgently

needed. Bonomo *et al.*^[17] showed that mice fed a Western diet developed indices of PN that were attenuated by concurrent fecal microbiome transplantation (FMT). And the author found changes in expression of genes involved in lipid metabolism and calcium handling in cells of the peripheral nerve system (PNS). FMT induced changes in the immune cell populations of the PNS. There was a correlation between an increase in the circulating SCFAs butyrate and pain improvement following FMT. The data suggested that FMT from lean to obese, insulin-resistant mice decreases obesity-induced hypersensitivity and increases nerve density in the skin. The results suggested that circulating butyrate, a metabolite secreted by gut microbiome and absorbed in the blood stream, may be involved by acting directly on PNS immune cells and gene expression or pain channels. Targeting the gut microbiome, butyrate, and its consequences may represent novel viable approaches to prevent or relieve obesity-associated neuropathies.

COMORBID BRAIN DISORDERS ASSOCIATED WITH DIABETES

Carbohydrate metabolism characteristics in Meniere's disease patients

Glucose and insulin profiles and their correlation in Meniere's disease patients were investigated in 64 patents. D'Avila *et al.*^[18] demonstrated 72% of them had some variable degree of hyperinsulinemia as show by their plasma insulin curves, whereas alterations on the glucose curve (reactive hypoglycemia or hyperglycemia) were found for only 21%. The author found a very strong correlation between insulin concentration measured by chemo-luminescence and by radioimmunoassay; the latter, however, showed values 1.3 times higher than those measured by chemo-luminescence.

Effect of hyperinsulinism on sensorineural hearing impairment in Meniere's disease

The comparison of the degree of sensorineural hearing loss in patients with Meniere's disease (MD) with and without hyperinsulinism by different methods of assessment was demonstrated by Lavinsky *et al.*^[19]. In the patients, 457, with a definite diagnosis of MD based on the American Academy of Otolaryngology-Head and Neck Surgery guidelines, 49 (76.6%) patients were defined as hyperinsulinemic and 15 (23.4%) were defined as normoinsulinemic. In patient with MD, there was a moderate correlation between the severity of hyperinsulinism, as defined by the 5-hour insulin curves, and other diagnostic methods used to assess insulin resistance in fasting samples. In conclusion, the author showed that hyperinsulinism in MD is associated with greater clinical hearing damage.

COMORBID BRAIN DISORDERS ASSOCIATED WITH DIABETES: THERAPEUTIC POTENTIALS OF PRE-/PRO-BIOTICS

Glucose metabolism play an important role related in neuro-energetics, neurotransmission, energy storage, biosynthesis and oxidative defense. Thus, tight regulation of glucose metabolism is critical for normal brain physiology. An exaggerated symptom of depression, anxiety, and cognitive deficits are shown in diabetic animal models as well as in a population-based study. Gut microbiota involve in the modulation of various physiological and pathological conditions of metabolic disorders and mental health by influencing the regulation of energy balance and release of neurotransmitters. Presently, no specific pharmacotherapies are available for CNS

comorbidities associated with diabetes. Some pre-/pro-biotics are playing promising role in management of these CNS complications. SCFAs affect the host's metabolism in several ways, for example SCFAs dependent activation of G-protein coupled receptor 41 (Gpr41) induces the expression of peptide YY, an intestinal hormone that inhibits gut motility, increases intestinal transit rate, and reduces the harvest of energy from the diet^[20]. Comorbid brain disorders associated with diabetes was reviewed by Thakur *et al*^[21]. The evidence-based studies through translational research and clinical setup are warranted for better understanding for the relationship between brain, glucose homeostasis and CNS complication as well as development of poly-pharmacologically active therapeutic drugs for the management of comorbid disorders associated with diabetic patients.

INNER EAR INSULIN RESISTANCE MIGHT CONTRIBUTE IN DIABETES-ASSOCIATED INNER EAR DYSFUNCTION

The evaluation of the impact of obesity/insulin resistance on inner ear fluid homeostasis *in vivo*, and the investigation whether the organ of Corti could be a target tissue for insulin signaling using auditory House Ear Institute-Organ of Corti 1 (HEI-OC1) cells as an *in vitro* model were demonstrated by Palbrink *et al*^[22]. The author found that insulin impacted on inner ear functions by mechanism classically associated with insulin signaling in target cells. In conclusion, the organ of Corti could be a target tissue for insulin action, and inner ear insulin resistance might contribute to the association between diabetes and inner ear dysfunction.

THE IMPACT OF TYPE2 DIABETES MELLITUS (T₂DM) ON THE ABNORMAL BLOOD FLOW ALTERATIONS IN TINNITUS PATIENTS

Meniere's disease represents a chronic disorder of inner ear and is characterized by recurrent vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. Both tinnitus and T₂DM are linked with cognitive decline and brain dysfunction. Xia *et al*^[23] examined the abnormal cerebral blood flow (CBF) patterns existed in tinnitus patients (60 patients and 40 non-tinnitus subjects) and potential relationships between the abnormal CBF and cognitive performance. In conclusion, tinnitus affects brain perfusion in the auditory area and default mode network. T₂DM and uncontrolled glucose levels may aggravate a CBF decrease in tinnitus patients. These findings implied that tinnitus patients may benefit from blood glucose control in terms of their cognitive function and tinnitus distress.

Gut microbial diversity, along with specifically butyrate-producing bacteria, may play a role in the development of Type 2 diabetes (T₂DM)

To examine associations of gut microbiome composition with insulin resistance and T₂DM in a large population-based setting controlling for various sociodemographic and lifestyle factors, Chen *et al*^[24] analyzed association among α -diversity, β -diversity, and taxa with the homeostatic model assessment of insulin resistance and with T₂DM from January 1, 2018 to December 31, 2020. In the cross-sectional study of 2166 participants in 2 large population-based studies, higher microbiome Shannon index and richness were associated with less insulin resistance, and patients with T₂DM ($n = 193$) had lower richness than participants without diabetes. And 12

groups of butyrate-producing bacteria were significantly linked to insulin resistance or T₂DM. These findings suggest that gut microbial diversity, along with specifically butyrate-producing bacteria, may play a role in the development of T₂DM, and could help provide insight into the etiology, pathogenesis, and treatment of T₂DM.

THE MICROBIOTA-GUT-BRAIN AXIS: A KEY PLAYER IN THE REGULATION OF VESTIBULAR DEFICIT

Vestibular deficit is a very common disorder in clinical practice and is characterized by vertigo, spontaneous nystagmus and autonomic nervous symptoms. Emerging evidence was shown that the microbiota-gut-brain axis play a key role in the regulation of affective disorders. To verify this hypothesis, Li *et al*^[25] constructed a unilateral labyrinthectomy mouse model to simulate vestibular deficit, and analyzed the microbiome and metabolome of the cecal samples collected from mice in the unilateral labyrinthectomy, sham surgery, and control groups. The altered microbes and metabolites were closely related to the pathogenesis of affective disorders. The results not only offered novel insight into the vestibular deficit comorbid with anxiety but also build an important basis for future research on this etiology. In our previous case report of *Aloe vera* juice (AVJ) ingestion on autism spectrum disorder, attention-deficit hyperactivity disorder, insomnia and Basedow's disease, we reported the improvement of chronic headache disorder; so-called migraine in 48-years of female, and otitis media and sinusitis in 13-years old male with successive injection of AVJ^[26].

CASE REPORTS

Case report 1: Recuperation from Meniere's disease (MD) with MD-medicine and AVJ ingestion

A 72-years old female who was obese (BMI > 25.0) and hypotensive (Blood pressure: lower than 129 mmHg and 84 mmHg) with her physical pain, was diagnosed MD on December, 1996. She started to take MD medicine with AVJ (daily 350 ml) ingestion. Since then, she alleviated MD symptom and menstrual cramps, and recovered with MD medicine and AVJ ingestion. She had no blood circulation trouble and cough for several years and had a well-being QOL on May, 2021.

Case report 2: Recovery from fatigue, tinnitus and paradoxical healing response with Kampo medicine: Hange-byakuzuyutu-tenmato and AVJ ingestion.

A ~50-years old female who had stress, tinnitus, and paradoxical healing response, was administered Hange-byakuzuyutu-tenmato; a typical Kampo medicine for the patients indicating water stasis, and ingested aloe vera juice (AVJ, 300ml) on January, 2020. She got much better condition on February, 2020 and she took only AVJ and is well-being of QOL on April, 2022.

Case report 3: Improvement of the patterns indicating blood stasis with Kampo medicine: Ketsupu-chikuo-gan with AVJ ingestion.

A ~50-years old male who had tinnitus and headache, was administered Ketsupu-chikuo-gan, a typical improving blood stasis Kampo medicine. But he did not recover and still had severe tinnitus. He was diagnosed as cerebrovascular disorder, and hospitalized on September, 2016, and operated on cerebral hemorrhage on December, 2016. Since then, he has been undertaken rehab and daily ingested

AVJ, and had a well-being QOL without tinnitus, headache and sequelae on May, 2022.

Case report 4: Recuperation from a sudden deafness with CoQ10 with AVJ ingestion

A ~70-years old female who had a sudden deafness on left ear, and tinnitus and paradoxical healing response on right ear on October, 2019. Then she administered Hange-byakuzyutu-tenmato, a typical Kampo medicine for the patient indicating water stasis, on December, 2019. She had a well response on right ear but still had tinnitus on left ear. Then, she cancelled administration of Kampo medicine and started ingestion of CoQ₁₀ 300mg/day with AVJ 300ml/day on April, 2022. She recovered from deafness and has well-being QOL on May, 2022.

SUMMARY

We discussed the current knowledge focusing on the influence of butyrate fermented in Aloe vera gel by which the gut-microbiota is beneficial for brain and behavior to homeostasis. Long-term successive ingestion of aloe vera juice may help to modulate the immune-sensitive via mitigation of pathogenesis and provide high concentration of the butyrogenic microbiome, such as *Faecalibacterium* spp. in the fecal host gut^[27]. In case reports, we demonstrated the recuperation of MD with MD-medicine and AVJ ingestion as an adjuvant, and the improvement of paradoxical healing response and tinnitus with Kampo medicine and AVJ/CoQ₁₀ ingestion. AVJ ingestion may support a poor water and blood circulation of Kampo medicine and CoQ₁₀ as an adjuvant^[28].

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