

Fermented Butyrate of Aloe vera and *A. arborescens* by Endophytic Bacteria: Its Prophylactic Action on Brain Insulin Resistance

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ABSTRACT

In this review, we documented prophylactic roles of butyric acid fermented by endophytic bacteria in *Aloe vera* and *A. arborescens* leaves on brain-gut microbiota cooperation in healthy aging.

Key words: Aloe plants; Fermented butyrate; Brain-insulin-resistance

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INTRODUCTION

Endophytic bacteria are microbes that colonize the internal tissues of plant without causing any immediately overt negative effects. A medicinal plant *Aloe vera* was explored for endophytic actinomycetes diversity, plant growth promoting and antimicrobial activity by Gangwar *et al*^[1]. Endophytic bacteria can produce novel antibiotic compounds and other secondary metabolites. They are considered as a promising source of new natural drug leads that are of great potential for medicinal and agricultural applications. Barra *et al*^[2] isolated *Talaromyces wortmannii*, as an endophyte of *A. vera* healthy tissue, and identified anti-biotoxic active biomodin, a symmetrical dimer of two emodin units. Kim *et al*^[3] revealed that five novel *Lactobacillus brevis* strains; probiotics originating from *A. vera* leaf, were isolated from naturally fermented *A. vera* leaf flesh, and expressed high levels of the glutamate decarboxylase gene which produces a beneficial neurotransmitter, γ -aminobutyric acid. Akinsanya *et al*^[4] isolated twenty-nine cultivable bacterial endophyte from *A. vera* surface-sterilized tissues and revealed the bioactive compounds with high DPPH scavenging properties and antimicrobial activities against bacterial pathogens. Nafis *et al*^[5] isolated an endophytic actinobacteria, NAF-1, similar to *Streptomyces hydrogenans* from *A. vera* leaves. The crude extract of the isolated strain showed a high anti-microbial and antioxidant activity. Endophytic actinomycetes were isolated from leaves of *A. arborescens*, collected in Moscow and Moscow region. To isolate rare actinomycetes microbiota, Machavariani *et al*^[6] used a modified method consisted in the pretreatment of leaves with solution of biologically active substances of plant origin: hetero-auxin and zircon. Using the modified method the authors identified *Nocardiopsis* genera; *Staphylococcus*, *Micrococcus* and *Bacillus* species in *A. arborescens* leaves.

A compelling set of links between the composition of the gut microbiota, the host diet, and host physiology has emerged. Gut

microbiota has been proven to be crucial importance in maintaining human health. Gut microbiota interacts with various organs and systems in the body, including brain, lung, liver, bone, cardiovascular system, and others. Nutrigenomics is a rapidly expanding field that elucidates the link between diet-genome interactions. Acetylation-mediated histone protein modification plays an important role in the epigenetic regulation of gene expression. Histone modification is controlled by the balance between histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes. Imbalance between the activities of these two enzymes is associated with various forms of cancer. Histone deacetylase inhibitors (HDACi) regulate the activity of HDACs and are being used in cancer treatment either alone or in combination with other chemotherapeutic drugs/radiotherapy. Sign *et al*^[7] summarized the HDACi classification, their aberrant expression in cancerous tissue, structures, sources, and the anticancer mechanisms of HDACi, as well as HDACi that are either FDA-approved or under clinical trials. Recent evidence demonstrates that regulation of the epigenome, and in particular inhibition of HDACs, impact pathogenic mechanisms involved in chronic disease. Godoy *et al*^[8] investigated a library of 131 natural compounds to determine bioactive compounds that inhibit Zn-dependent HDAC activity.

Vagal afferents serve to link intestinal information to the brain. Goswami *et al*^[9] explored a possible role of vagal afferents in the anorexigenic effect of SCFAs. Intraperitoneal injection of three SCFAs molecules suppressed food intake in fasted mice with the rank order of butyrate>propionate>acetate. Moreover, butyrate directly interacted with single neurons isolated from nodose ganglia and induced intracellular Ca²⁺ signaling. The results identify the vagal afferent as the novel pathway through which exogenous SCFAs execute the remote control of feeding behavior and possibly other brain functions. Vagal afferents might participate in suppression of intestine-born SCFAs.

Changes in histone and non-histone protein acetylation play a key role in protein structure and function that can alter other post translational modifications (PTMs), including protein phosphorylation. Protein phosphorylation is a well described PTM that is important for cardiac signal transduction, protein activity and gene expression, yet the functional role for acetylation-phosphorylation cross-talk in the myocardium remains less clear. Habibian *et al*^[10] provided the regulation and function for acetylation-phosphorylation cross-talk in the heart, with a focus on the role for HDACs and HDAC inhibitors as regulators of acetyl-phosphorylation cross-talk in the control of cardiac function. We review in this paper is to provide fresh insights as to *Aloe's* immune modulation due to butyrate fermented by the dietary *Aloe* in the gut on brain insulin resistance.

INFLUENCE OF ALOE VERA AND *A. ARBORESCENS* ON NEURONAL DISORDERS

Historically insulin was thought solely to be a peripherally acting hormone responsible for glucose homeostasis and energy metabolism. However accumulating evidence indicates insulin can cross the blood-brain-barrier and influence a multitude of process in the brain including neuronal survival and growth, maintenance of synapses and pathways involved in cognition. In elderly people, the diversity of the gut microbiota is reduced and there is an increased incidence of degenerative disease, including Alzheimer's disease and Parkinson's disease^[11]. Halder *et al*^[12] explored the effect of *A. vera* in animal models of learning and memory, the passive avoidance task and elevated plus-maze were tested. *A. vera* significantly reduced the

transfer latency as compared to control. The authors showed that *A. vera* enhances learning and memory, and also alleviates depression in mice.

Oxidative of stress has a major role in progression of diabetes-related behavioral deficits. It has suggested that *Aloe vera* has anti-diabetic, anti-oxidative, and neuroprotective effects. Tabatabaei *et al*^[13] investigated the effect of *A. vera* gel on behavioral functions, oxidative status, and neuronal viability in the hippocampus of streptozotocin-induced diabetic rats. The changes in diabetic rats were accompanied by increasing oxidative stress and neuronal loss in the hippocampus. Furthermore, eight weeks of treatment with *A. vera* gel not only alleviated all the mentioned deficits related to diabetes, but in some aspects, was even more effective than insulin. These results suggested that both interrelated hypoglycemic and anti-oxidative properties of *A. vera* gel are possible mechanisms that improve behavioral deficits and protect hippocampal neurons in diabetic animals. The clinical syndrome of Parkinson's disease (PD) results from idiopathic degeneration of the dopaminergic cells in the pars compacta of the substantia nigra. While the cause of the degeneration of the dopaminergic cells in the pars compacta of the substantia nigra is not known, oxidative stress plays an important role. Investigation of antiparkinsonian effect of *A. vera* on haloperidol induced experimental animal model was demonstrated by Bagewadi *et al*^[14]. The results conclusively showed that *A. vera* has beneficial effect in haloperidol induced experimental model of PD.

Clementi *et al*^[15] provided evidence that *A. arborescens* extract protects IMR32, a neuroblastoma human cellular line, from toxicity induced by β -amyloid, the peptide responsible for Alzheimer's disease (AD). The protective mechanism exerted by *A. arborescens* seems be related to lowering of oxidative potential of the cells, as demonstrated by the ROS measurement compared with the results obtained in the presence of A β (1-42) alone. It was suggested that use of *A. arborescens* extract could be developed as agents for the management of AD. Abbaoui *et al*^[16] evaluated the impact of acute Cu intoxication for 3days on the dopaminergic system and locomotor performance, together with the possible restorative effect of oral administration of aqueous extract of *A. arborescens* gel. The present investigation have brought, on the one hand, an experimental evidence of an altered dopaminergic innervations following Cu intoxication and on the other hand, a new pharmacological property of *A. arborescens* that may be used as a neuroprotective plant for neurodegenerative disorders, such as PD, touching the dopaminergic system triggered by heavy metals. Lewis *et al*^[17] reported the effect of an aloe polymannose multi-nutrient complex formula on cognitive and immune functioning over 12 months among adults diagnosed with AD. The authors showed improvements in both clinical and physiological outcomes for a disease that otherwise has no standard ameliorative remedy. Dietary fibers are metabolized by gastrointestinal bacteria into SCFAs. Ho *et al*^[18] investigated the potential role of these SCFAs in A β mediated pathological processes that play key roles in AD pathogenesis. Multiple complementary assays were used to investigate individual SCFAs for their dose-responsive effects in interfering with the assembly of A β 1-40 and A β 1-42 peptides into soluble neurotoxic A β aggregates. The studies support the hypothesis that intestinal microbiota may help protect against AD, in part, by supporting the generation of selected SCFAs, which interfere with the formation of toxic soluble A β aggregates. SCFAs act not only locally in the intestines colonized by commensal bacteria, but also influence the intestinal immune cells, and modulate immune response by multi-protein inflammasome complexes. Ratajczak *et al*^[19] reviewed that SCFAs have been confirmed to

contribute to the maintenance of the immune homeostasis of the urinary system (kidney), respiratory system (lungs), central nervous system, and the sight organ.

BRAIN INSULIN RESISTANCE IN ALZHEIMER'S DISEASE (AD), PARKINSON'S DISEASE (PD), AND DEPRESSION

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that includes obesity, diabetes, and dyslipidemia. Accumulating evidence implies that MetS contributes to the development and progression of AD. Insulin resistance (IR) is at the core of MetS and likely represents the key link between MetS and AD. In the central nervous system, insulin plays key roles in learning and memory, and AD patients exhibit impaired insulin signaling that is similar to that observed in MetS.

Increased dietary fiber consumption has been associated with many beneficial effects, including amelioration of obesity and insulin resistance. These effects may be due to the increased production of SCFAs during fermentation of the dietary fiber in the colon. Jiao *et al.*^[20] applied a meta-analysis to obtain an unbiased evaluation of structural and functional changes of gut microbiota in diet-induced obese rodents. Differential functional pathways of the gut microbiome in obese rodents included enriched pyruvate metabolism, butanoate metabolism, propanoate metabolism, pentose phosphate pathway, fatty acid biosynthesis, and glycerolipid metabolism pathways. These pathways converge in the function of carbohydrate metabolism, SCFA metabolism, and biosynthesis of lipid. The altered gut microbiome may contribute to obesity development by promoting insulin resistance and systemic inflammation. Bolzabadi *et al.*^[21] conducted the randomized, double-blind, placebo-controlled clinical trial. Patients were randomly allocated into two groups to take either 8×10^9 CFU/day probiotic supplements of placebo ($n = 25$ each) group, one capsule daily for 12 weeks.

Probiotics supplementation for 12 weeks in PD patients significantly improved gene expression of IL-1, IL-8, TNF- α , TGF- β and PPAR- γ , but did not affect gene expression of VEGF and LDLR, and biomarkers of inflammation and oxidative stress. McNabney *et al.*^[22] reviewed focuses on sources of SCFAs with emphasis on sources of butyrate, mechanisms of fiber and butyrate metabolism in the gut, and its protective effects on colon cancer, and the peripheral effects of butyrate supplementation in peripheral tissues in the prevention and reversal of obesity and insulin resistance. Kim *et al.*^[23] discussed MetS as a risk factor for AD, focusing on IR and future directions of insulin-based therapies. There is growing interest in the relationship of type 2 diabetes and its pathophysiological mechanisms with Alzheimer's disease (AD). The gut microbiota is known as a second genome because it includes microbes, genomic DNA, proteins, and metabolites. In elderly people, the diversity of the gut microbiota is reduced and there is an increased incidence of degenerative diseases, including AD and PD, and decreased cognitive and memory functions. In addition to decreased diversity, the changes of the gut microbiome composition to an imbalanced state, i.e. dysbiosis, also correlates with frailty, inflammation, and neurodegenerative disorders such as AD and PD in the elderly. The gut bacteria producing metabolites like SCFAs are frequently reduced in patients with diabetes, obesity, autoimmune disorders, and cancers. Nagpal *et al.*^[24] developed a human-origin probiotic cocktail with the ability to modulate gut microbiota to increase native SCFA production. The authors indicated that human-origin probiotic *Lactobacilli* and *Enterococci* could ameliorate gut microbiome

dysbiosis and hence may prove to be a potential therapy for diseases involving reduced SCFAs production in the gut. PD is the most common movement disorder. In general, the clinical manifestations of PD result from dysfunction of the basal ganglia. Studies with HDAC inhibitors result in beneficial effect in both *in vivo* and *in vitro* models of PD. Various clinical trials have been initiated to investigate the possible therapeutic potential of HDAC inhibitors in patients suffering from PD. Sharma *et al.*^[25] discussed the putative role of HDAC inhibitors in PD and associated abnormalities and suggest new directions for future research in PD. In order to investigate the effect of diabetes mellitus (DM) on the clinic-radiological features in patients with PD, Chung *et al.*^[26] performed inter-group comparative analysis of the striatal dopamine transporter (DAT) availability in all patient and level of cognitive performances in 312 patients (58 with DM and 254 without). The patients with DM were older at the onset of parkinsonism and had more severely decreased baseline DAT availability in the caudate and ventral striatum than those without DM. The PD group with DM showed poor performances in attention/working memory and frontal/executive function than the group without DM. The authors suggest that coexistent DM may have a detrimental effect on disease progression as well as baseline striatal dopamine loss, brain structural alterations, and cognitive performances in patients with PD. Type 2 diabetes is a risk factor for several chronic neurodegenerative disorders such as AD or PD. The link appears to be insulin de-sensitization in the brain. Insulin is an important neuroprotective growth factor. Glucagon like peptide 1 (GLP-1) and glucose-dependent insulin-tropic polypeptide (GIP) are growth factors that re-sensitize insulin and GLP-1 mimetics are used in the clinic to treat diabetes. Reduced insulin signaling in the brain is a hallmark of AD patients, even in the absence of systemic type 1 or 2 diabetes, prompting some researchers to refer to AD as brain-specific, or type 3 diabetes. A key question that arises about this signature feature of AD is "how, if at all, does the brain's impaired ability to utilize insulin contribute to the behavioral deficits associated with AD?" Bloom *et al.*^[27] discussed how A β and tau work coordinately to deprive neurons of functionally accessible insulin receptors and dysregulate normal signal by the protein kinase, mTOR. Holsher^[28] showed novel dual GLP-1/GIP receptor agonists to neuroprotective effects in AD and PD models. GLP-1 and GIP mimetics initially designed to treat diabetes show good protective effects in animal models of AD and PD. Based on these result, several clinical trials have shown first encouraging effects in patients with AD or PD. Arnold *et al.*^[29] demonstrated profound insulin resistance in postmortem brain tissues from people with AD using a novel *ex vivo* insulin stimulation paradigm and further characterized abnormalities in the activation states of many insulin signaling pathway proteins in mild cognitive impairment patients, AD and mouse models. Neuronal insulin resistance was found in AD even in the absence of known diabetes, suggesting that insulin resistance may be an intrinsic pathophysiological feature of AD. The authors reviewed evidence of intrinsic brain insulin resistance in AD and related dementias, showing main characteristics of insulin signaling in neurons, astrocytes, microglia and the vascular system.

Hamer and Batty^[30] examined the association of body mass index (BMI) and waist-to-hip ratio (WHR) with brain volume. Measures included BMI, WHR, and total fat mass as ascertained from bio-impedance. Brain images were produced with structural magnetic resonance imaging. The combination of overall obesity and central obesity was associated with the lowest gray matter compared with that in lean adults. The authors suggest that the combination of heightened BMI and WHR may be an important risk factor for

gray matter atrophy. Neuropsychiatric disorders and type2 diabetes (T2D) are major public health concerns proposed to be intimately connected. T2D is associated with increased risk of dementia, neuropsychiatric and mood disorders. Evidences of the involvement of insulin signaling on brain mechanisms related to depression indicate that insulin resistance, a hallmark of T2D, could develop in the brains of depressive patients. Lyra E Silva *et al*^[31] discussed possible molecular mechanisms associating defective brain insulin signaling with reward system, neurogenesis, synaptic plasticity and hypothalamic-pituitary-adrenal stress axis in depression. Due to the high resistance rate of anti-depressants, novel insights into the link between insulin resistance and depression may advance the development of alternative treatments for this disease.

BRAIN-GUT-MICROBIOTA-MICROGLIA-SCFAS COOPERATION

SCFAs have recently been shown to influence the CNS by modulating microglia during maturation, homeostasis, and disease. Microglia are one of the four predominant cell types in the brain (neuron, glia, microglia, astrocyte), and are the principal immune cell of the brain, serving a macrophage-like function to defend against invading pathogens. Erny *et al*^[32] postulate that the microbiota guide microglia maturation and maintain a homeostatic never resting state in which cells are ready to fight invading pathogens or respond to danger signals, and their evidence suggests that SCFA signaling mediates this process. These findings suggest that host bacteria vitally regulate microglia maturation and function, whereas microglia impairment can be rectified to some extent by complex microbiota. Sampson *et al*^[33] demonstrated a functional link between gut bacteria and Parkinson Disease (PD). SCFAs were important in a model of PD using α -synuclein overexpressing (ASO) mice. ASO mice that were deficient in microbiota (Germ free; GF or antibiotic-treated) had fewer motor deficits than their conventional counterparts. Along with improved motor function, GF-ASO mice had morphological changes in microglial populations that resembled less-activated microglia (including a decreased cell diameter, with increased and longer processes), as well as lower levels of the pro-inflammatory cytokines IL-6 and TNF- α in brain regions relevant for PD. In order to test whether patients with PD harbored a microbiota that contributes to the disease, they transferred the microbiota of six new-onset, treatment-naïve patients with PD and the microbiota of six healthy controls to groups of GF mice. In five of the six pairs, the PD microbiota lead to worse motor deficits versus the healthy control microbiota, providing the first causal evidence that the microbiome may actively contribute to PD pathogenesis. These findings reveal that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiome represent a risk factor for PD. Tamtaji *et al*^[34] investigated randomized, double-blind, placebo-controlled clinical trial, which was done in sixty people with PD. Individuals were randomly divided into two groups in order to take either 8×10^9 CFU/day or placebo that lasted 12 weeks. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was recorded at pre- and post-intervention. The study evidenced that 12 weeks of probiotic consumption by individuals with PD had useful impacts on MDS-UPDRS and few metabolic profiles. Garcia *et al*^[35] demonstrated whether synthetic or endogenously produced butyrate can delay PD progression, attenuate PD associated gastrointestinal (GI) dysfunction, and impact the gut-microbiota in transgenic mice expressing human mutant α -Synuclein (α -Syn), mice expressing α -Syn A53T and α -Syn Y39C. The authors

showed that both sodium butyrate and sodium phenylbutyrate delay disease progression in α -Syn Y39C mice. A novel, highly accessible treatment with the potential to delay PD progression and target motor, cognitive, and GI deficits associated with PD was determined.

Microglia is tissue macrophage of the central nervous system (CNS). Microglia persists in the CNS throughout the life of the organism and self-renew without engraftment of bone-marrow-derived cells. Microglia functions under homeostatic conditions and its modulation by host microbiota. During adulthood cortical microglia mature neurons and are involved in learning-induced dendritic spine formation and nourish neurons. Furthermore, colony-stimulating factor 1, interleukin-34 and SCFAs are important components for microglia function and maturation. Erny *et al*^[36] discussed new aspects of the interaction between host microbiota and brain function with special focus on the brain-resistant innate immune cells, the microglia. Butyrate positively modulates mitochondrial (Mtc) function, including enhancing oxidative phosphorylation and β -oxidation and has been proposed as a neuro-protectant. Butyrate and other SCFAs have also been associated with autism spectrum disorders (ASD), a condition associated with Mtc dysfunction. Rose *et al*^[37] have developed a lymphoblastoid cell line (LCL) model of ASD, with a subset of LCLs demonstrating Mtc dysfunction and another subset of LCLs demonstrating normal Mtc function. The authors measured Mtc function in ASD and age-matched control LCLs, all derived from boys, following 24 and 48 h exposure to butyrate both with and without an *in vitro* increase in ROS. It was shown that the enteric microbiome-derived SCFA butyrate modulates Mtc activity, with this modulation dependent on concentration, microenvironment redox state, and the underlying Mtc function of the cell. Butyrate can enhance Mtc function in the context of physiological stress and/or Mtc dysfunction, and may be an important metabolite that can help rescue energy metabolism during disease states. Thus, insight into this metabolic modulator may have wide application for both health and disease since butyrate has been implicated in a wide variety of conditions including ASD. Cumulative evidence reveals that the gut microbiota and its metabolites, SCFAs play an important role in GI disorders and the pathogenesis of ASD. Liu *et al*^[38] found lower levels of fecal acetic acid and butyric acid and a higher level of fecal valeric acid in ASD subjects. The authors identified decreased abundances of key butyrate-producing taxa and an increasing abundance of valeric acid associated bacteria among autistic individuals. Constipation was the only gastrointestinal disorder in ASD children. It was suggested that the gut microbiota contributes to fecal SCFAs and constipation in autism. Modulating the gut microbiota, especially butyrate-producing bacteria, could be a promising strategy in the search for alternative for the treatment of autism spectrum disorder.

SUMMARY

The association between the fecal microbiome and insulin sensitivity and secretion was examined using gold-standard methods in high-risk populations prior to diabetes onsets by Naderpoor *et al*^[39]. The results suggest that fecal microbiota is related to insulin sensitivity and secretion in overweight or obese adults. Alterations in intestinal microbiota composition could promote a proinflammatory state in adipose tissue that is associated with obesity and insulin resistance. Moreno-Indias *et al*^[40] identified the gut microbiota associated with insulin resistance in appendix samples from morbidly obese patients classified in 2 groups, high (IR-MO) and low insulin-resistant (NIR-MO), and determined the possible association between these gut

microbiota and variables associated with insulin resistance and the expression of genes related to inflammation and macrophage infiltration in adipose tissue. Appendix dysbiosis occurs in IR-MO patients, with a loss of butyrate-producing bacteria, essential to maintenance of gut integrity, together with an increase in mucin-degrading bacteria and opportunistic pathogens. The microbiota present in the IR-MO group were related to low grade inflammation in adipose tissue and could be useful for developing strategies to control the development of insulin resistance. Using “healthy” aging mice and macaques, Bodogai *et al.*^[41] found that insulin resistance (IR) was induced by activated innate 4-1BBL⁺ B1a cells. These cells (4BL cells) accumulated in aging in response to changes in gut commensals and a decrease in beneficial metabolites such as butyrate. The authors found evidence suggesting that loss of the commensal bacterium *Akkermansia muciniphila* impaired intestinal integrity, causing leakage of bacterial products such as endotoxin, which activated CCR2⁺ monocytes when butyrate was decreased. The results underscore the pathological function of B1a cells and suggest that the microbiome-monocyte-B cell axis could potentially be targeted to reverse age-associated IR.

Decreased diversity, considered an indicator of an unhealthy microbiome, has been linked to different chronic conditions such as obesity, type2 diabetes and insulin resistance. In addition to decreased diversity, the changes of the gut microbiome composition position to an imbalanced state, i.e. dysbiosis, also correlates with frailty, inflammation, and neurodegenerative disorders such as AD and PD in the elderly. Kong *et al.*^[42] found that cohort study of long-living people possesses a more diverse gut microbiota than younger adults. They also found a group of bacteria, members of which are known SCFA producers such as *Clostridium* cluster XIVa, are enriched in the long-living Chinese. Furthermore, they showed that the greater gut microbiome diversity in the long-living people was also observed in two more independent cohorts: one from Jiangsu, China and the other from Japan^[43].

Aging in human is associated with a reduction in the beneficial commensal microbes, which control expansion of pathogenic commensals and maintain the integrity of the intestinal barrier through the production of mucus and lipid metabolisms, such as short chain fatty acids (SCFAs); butyric acid. Alterations in gut microbiota might be accompanied by altered concentrations of SCFAs. Thus, interventions that alter the composition of the gut microbiota might reduce pro-inflammatory state and rejuvenate immune functions to provide anticancer and insulin secretion benefits in frail elderly people.

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