

Association of Butyrate Fermented in Aloe Vera Gel With Alzheimer's Disease and Dementia Progression. Case Report 1: Mitigation of Nursing Care Level

Akira Yagi¹, PhD; Megumi Hasegawa², Suzuka Ataka³, MD, PhD

¹ Special advisor of Japan Aloe Science Association; Editor-in-Chief of Journal of GHR; Professor Emeritus of Fukuyama University, Hiroshima, Japan;

² Pharmacist, Kampo Pharmacy Grace-Meg-Salon, Toshima-ku, Tokyo, Japan;

³ The director of Med Cell Clinic, Umeda, Kita-ku, Osaka, Japan.

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Correspondence to: Akira Yagi, 2-10-1 Hanagaura-ku, Kasuyamachi, Kasuya-gun, Fukuoka-ken, Japan 811-2310.

Email: 0131akirayagi@gmail.com

Telephone: +81-92-938-2717

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ABSTRACT

The non-digestible polysaccharide acemannan in Aloe vera gel is highly butyrate fermentable dietary fiber. The relationship between Alzheimer's disease and related dementia with butyrogenic microbiota and butyrate fermented was discussed in the prevention of human physiological disease such as Alzheimer's disease and dementia progression. In case report 1, it was suggested that the efficacy of hypotensive, hypoglycemic, antianginal, and cognition enhancer drug for a frail female patient needed the nursing care level 2, may be supported with daily ingestion of aloe vera juice with the drug and multivitamin modulating from the nursing care level 2 into 1 and providing an important role in the modulation of brain homeostasis.

Key words: Aloe vera gel; Butyrate fermented; Association of butyrate to Alzheimer's disease; Dementia progression

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INTRODUCTION

Alzheimer's disease is one of the leading causes of disability or death in the elderly worldwide and has become a serious health problem. Increasing clinical and preclinical evidence implicates the microbiome as a possible key susceptibility factor for neurological disorders, including AD, autism spectrum disorder, and Parkinson's disease. Emerging evidence suggests that gut dysbiosis can cause neurocognitive disorder such as depression and anxiety as well as the psychological, behavioral symptoms of dementia and Alzheimer's disease (AD). Studies of the intestinal microbiome and AD have demonstrated associations with microbiome composition at the genes level among matched cohorts. Wu et al^[1] characterized the gut microbial metabolites among AD, amnesic mild cognitive impairment (aMCI) and dementia AD. The author found that microbial signatures could be noninvasive biomarkers for AD screening and management, and targeting intestinal microbiota or microbial metabolism might be a promising method for preventing and treating AD. The gut microbiome (GM) and microbial dysbiosis contribute to some of the more prevalent mental health and neurocognitive disorders (Shabbir et al^[2]). Scoping review by Halverson et al^[3] about the effect of GM on neurocognitive and mental health disorders, found that gut dysbiosis is seen in various mental health conditions. Various psychotropic medications can have an influence on the gut microbiota by their antimicrobial effect. Research into the role of GM in modulating brain function has rapidly increased over the past 10 years, albeit chiefly in animal models. Altered gut microbiota in a mouse model of AD was examined by Zhang et al^[4]. The level of short chain fatty acids (SCFAs) is reduced in mouse models of AD. Concentrations of butyrate, and isobutyrate

in particular, were reduced in both feces and brain of AD [APP^{swe}/PS1^{ΔE9} (PAP)] transgenic male mice. Colombo *et al.*^[5] identified microbiota-derived SCFAs as microbial metabolites which promote Aβ deposition. Germ-free (GF) AD mice exhibit a substantially reduced Aβ plaque load and markedly reduced SCFAs plasma concentrations; conversely, SCFAs supplementation to GF AD mice increased the Aβ plaque load to level of conventionally colonized specific pathogen-free (SPF) animal and SCFAs supplementation to SPF mice even further exacerbated plaque load. The results demonstrated that microbiota-derived SCFAs are critical mediators along the gut-brain axis which promote Aβ deposition likely via modulation of the microglial phenotype. Colombo *et al.*^[6] found that microbiota-derived SCFAs modulate microglia and promote Alzheimer β (Aβ) plaque deposition. Supplementation of SCFAs to germ-free APPS1 mice nearly doubled the cerebral Aβ plaque load potentially through modulation of the microglial phenotype identified microbiota-derived SCFA as key metabolites along the gut-brain axis in AD. Germ-free (GF) AD mice exhibited a substantially reduced Aβ plaque load and markedly reduced SCFA plasma concentrations; conversely, SCFA supplementation to GF AD mice was sufficient to increase the Aβ plaque load to level of conventionally colonized animals. The author identified SCFAs as key microbial metabolites contributing to AD progression via activation of microbial cells and upregulation of apolipoprotein E (ApoE). (ApoE is the recognition site for receptors involved in the clearance of remnants of very low density lipoproteins and chylomicrons). Thus, the author demonstrated that microbiota-derived SCFAs are the key mediators along the gut-brain axis resulting in increased microglial activation, ApoE upregulation and Aβ deposition. Govindarajan *et al.*^[7] showed that severe amyloid pathology correlated with a pronounced dysregulation of histone acetylation in the forebrain of APPS1-21 mice. The prolonged treatment with the pan-HDAC inhibitor sodium butyrate improved associative memory in APPS1-21 mice even when administered at a very advanced stage of pathology. The recovery of memory function correlated with elevated hippocampal histone acetylation and increased expression of genes implicated in associative learning. The data advanced the potential applicability of HDAC inhibitors for the treatment of AD and suggested that HDAC inhibitors may have beneficial effects even when administered long after the onset of disease-associated symptoms.

In previous paper we described prophylactic role of aloe components, butyrate fermented, micrans and hyaluronan on AD and Parkinson's disease and osteoarthritis in knee joints. And the successive ingestion of Aloe vera juice provided high concentration of the butyrogenic microbiome *Faecalibacterium* and *Clostridium* spp. in fecal of frail 61-years-old woman^[8]. In the present article, we described the beneficial effect of butyrate for the animal models and patients through regulating the gut microbiota-brain axis. In case report 1, it was suggested that the efficacy of hypotensive, hypoglycemic, antianginal and cognitive enhancer drug for a frail female patient, needed the nursing care level 2, may be supported with daily ingestion of aloe vera juice, the drug and multivitamin modulating from the nursing care level 2 into 1 and providing an important role in the modulation of brain homeostasis.

THE ROLE OF MICROBIAL METABOLITES PRODUCING SHORT CHAIN FATTY ACIDS IN GUT-BRAIN COMMUNICATION

In our previous paper we found that the ingestion of aloe vera juice for seven-years in 61-years old frail female increased *Clostridium*

2.4 fold higher, *Faecalibacterium* 3.4 fold higher, and *Lactobacillus* 2.0 fold higher, compared to the standard value^[8]. Both *Clostridium* and *Faecalibacterium* spp. is one of typical butyrogenic microbiome exhibiting the potent immune regulative function. The role of probiotics in preventing AD by regulating gut microbiota (GM)-gut-brain axis was studied by Sun *et al.*^[9]. The anti-neuro-inflammatory effect and its mechanism of probiotic *Clostridium butyricum* (CB) against AD is investigated by regulating GM-gut-brain axis. The author indicated that CB treatment prevents cognitive impairment, Aβ deposits, microglia activation, and production of tumor necrosis factor-α and IL-1β in the brain of APP^{swe}/PS1^{ΔE9} (APP/PS1) mice, suggesting that CB treatment could attenuate microglia-mediated neuro-inflammation via regulating the GM-gut-brain axis, which is mediated by the metabolite butyrate.

THE EFFICACY OF FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Sun *et al.*^[10] evaluated the efficacy of fecal microbiota transplantation (FMT) for the treatment of AD, using an APP/PS1 transgenic mouse model. The results showed that FMT treatment could improve cognitive deficits and reduced the brain deposition of Aβ in APP/PS1 transgenic mice. The author suggested that the mechanism of anti-AD may be related to the increase of SCFAs, butyrate and FMT may be a potential therapeutic strategy for AD.

Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation

Hazan^[11] presented symptom improvement in a patient with Alzheimer's disease following fecal microbiota transplantation for a *Clostridioides difficile* (*Clostridium difficile*) infection in case report. In our previous case report paper, we described that the ingestion of *Aloe vera* juice (AVJ) for seven-years in 61-years old frail female increased 3.4 and 2.4 fold higher in the comparative fecal concentration of butyrogenic prebiotic *Faecalibacterium* spp. and *Clostridium* spp. respectively^[8]. Our case report suggested successive intake of AVJ keeps healthy life and well QOL.

THE ROLE OF SHORT CHAIN FATTY ACIDS IN Aβ MEDIATED PATHOLOGICAL PROCESSES

Multiple complementary assays were used by Ho *et al.*^[12] to investigate individual SCFAs for their dose-responsive effects in interfering with the assembly of Aβ1-40 and Aβ1-42 peptides into soluble neurotoxic Aβ aggregates. The author suggested that intestinal microbiota may help protect against AD by supporting the generation of select SCFAs, which interfere with the formation of toxic soluble Aβ aggregates.

THE NEUROPROTECTIVE EFFECTS OF BUTYRATE AND THE DISEASES WHICH MAY BENEFIT FROM BUTYRATE TREATMENT OR A HIGHER FIBER DIET

The role of short chain fatty acids in disorders of the microbiota-gut-brain axis

Ongoing research was focused on the entry of SCFAs into systemic circulation from the gut lumen, their migration to cerebral circulation and across the blood brain barrier and their potential to exert acute

and chronic effects on brain structure and function by O’Riordan et al^[13]. The author discussed that SCFAs have on brain function, behavior and physiology, which will inform future microbiota-targeted interventions for brain disorders.

Butyrate can protect the brain and enhance plasticity in neurological disease models

Butyrate has been extensively studied as a histone deacetylase inhibitor but also functions as a ligand for a subset of G-protein-coupled receptors and as an energy metabolite. Butyrate can protect the brain and enhance plasticity in neurological disease models. Bourassa et al^[14] integrated evidence from the disparate fields of gastroenterology and neuroscience to hypothesize that the metabolism of high fiber diet in the gut can alter gene expression in the brain to prevent neurodegeneration and promote regeneration.

SODIUM BUTYRATE IMPROVING THE ASSOCIATIVE MEMORY OF ALZHEIMER’S MOUSE MODEL

A β plays an important role in the pathogenesis of AD. Sodium butyrate (NaB) exerts neuroprotective effects such as anti-inflammatory, antioxidant, anti-apoptotic, and cognitive improvement in central nervous system diseases. Sun et al^[15] aimed to research the protective effects of NaB on neurons against A β toxicity and to uncover the underlying mechanisms. The results showed that 2mM NaB had a significant improvement effect on A β -induced N2a cell injury, by increasing cell viability and reducing ROS to reduce injury. And by acting on the GPR 109A receptor, NaB regulates the expression of AD-related genes such as APP, NEP, and BDNF. (AD-related genes: APP; Amyloid precursor protein. NEP: Neprilysin, the main cleavage enzyme of A β . BDNF: Brain derived neurotrophic factor). NaB protects N2a cells from A β -induced cell damage through activating GPR 109A, which provides an innovative idea for the treatment of AD. Fernando et al^[16] investigated the ability of the histone deacetylase inhibitor NaB to attenuate memory deficits in the 5xFDA mouse model of AD following a 12-week feeding regimen. NaB had profound effects on A β levels and on associative learning and cognitive functioning. A 40% reduction on brain A β levels and a 25% increase in fear response in both the cued and contextual testing was observed in the NaB-treated animals compared to the control group on associative learning and cognitive functioning.

BEHAVIORAL TESTING OF FECAL TRANSPLANTED GERM-FREE MICE IN A BIOSAFETY CABINET

The gut microbiome and the gut brain axis are potential determinants of AD etiology or severity. Using 6-month-old human amyloid precursor protein (hAPP) knock-in (KI) mice, which contain the Swedish and Iberian mutation [APP NL-F (*APP^{NL-F}*)] or the Arctic mutation as third mutation [APP NL-G-F (*APP^{NL-G-F}*)], behavioral and cognitive performance is associated with the gut microbiome and APP genotype modulates this association. Kundu et al^[17] determined the feasibility of behavioral testing of mice in a biosafety cabinet and whether stool from 6-month-old *APP^{NL-G-F}* mice or *APP^{NL-G-F}* crossed with human apoE4 targeted replacement mice is sufficient to induce behavioral phenotypes in 4-5 month-old germ-free C57BL/6J mice 4 weeks followed inoculation. The author compared the behavioral

phenotypes of the recipient mice with that of the donor mice, and finally, assessed cortical A β levels and analyzed the gut microbiome in the recipient mice. The author found that behavioral testing of fecal transplanted germ-free mice in a biosafety cabinet is feasible and stool from *APP^{NL-G-F}* and *APP^{NL-G-F/E4}* mice is sufficient to induce behavioral phenotypes in germ-free C57BL/6J mice 4 weeks following inoculation, and the relationship between cortical insoluble human A β 40 levels and activity levels in the open field is also genotype-dependent.

THE ALZHEIMER’S DISEASE MICROBIOME ASSOCIATED WITH DYSREGULATION OF THE ANTI-INFLAMMATORY P-GLYCOPROTEIN PATHWAY

The characteristic bacterial taxonomic composition of fecal samples from participants with and without a diagnosis of dementia due to Alzheimer’s disease

Vogt et al^[18] analyzed that the gut microbiome of AD participants has decreased microbial diversity and is compositionally distinct from control age- and sex-matched individuals. The author identified phylum-through genus-wide differences in bacterial abundance including decreased *Firmicutes*, increased *Bacteroidetes*, and decreased *Bifidobacterium* in the microbiome of AD participants. The intestinal microbiota of AD patients revealed that their microbiome differs from that of subjects without dementia.

The Alzheimer’s disease microbiome associated with inflammatory P-glycoprotein pathway

Haran et al^[19] prospectively enrolled 108 nursing home elders and followed each for up to 5 months, collecting longitudinal stool samples from which the authors performed metagenomics sequencing and in vitro T84 intestinal epithelial cell functional assays for P-glycoprotein (P-gp). P-gp expression is a critical mediator of intestinal homeostasis. (P-gp: a 170.000-dalton plasma cell membrane glycoprotein is one of the drug transporters that determine the uptake and efflux of a range of drugs. Efflux transporters play an important role in drug transport in many organs. P-gp is one of the drug transporters that determine the uptake and efflux of a range of drugs). The author’s analysis identified clinical parameters as well as numerous microbial taxa and functional genes that act as predictors of A β dementia in comparison to elders without dementia or with other dementia types. And the author demonstrated that stool samples from elders with AD can induce lower P-gp expression levels in vitro those samples from elders without dementia or with other dementia types. Furthermore the author also paired functional studies with machine learning approaches to identify bacterial species differentiating the microbiome of AD elders from that of elders without dementia which in turn are accurate predictors of the loss of dysregulation of the P-gp pathway. The author observed that the microbiome of AD elders shows a lower proportion and prevalence of bacteria with the potential to synthesize butyrate, as well as higher abundances of taxa that are known to cause pro-inflammatory states. Therefore, a potential nexus between the intestinal microbiome and AD is the modulation of intestinal homeostasis by increases in inflammatory, and decreases in anti-inflammatory, microbial metabolism. The work provided an important advance to bridge the gap in how the AD microbiome can potentially adversely affect intestinal epithelial homeostasis via dysregulation of P-gp pathway.

A COHORT STUDY IDENTIFYING DIFFERENCES IN ALZHEIMER'S DISEASE (AD) FROM AMNESTIC MILD COGNITIVE IMPAIRMENT (A MCI) AND THE HEALTHY CONTROLS

Liu *et al*^[20] expressed the study identifying differences in microbiome between patients with 32 AD in pre-onset stage amnesic mild cognitive impairment, a MCI, 33 AD and the 32 normal cognitive healthy controls. Among bacterial taxa determined by 16S-ribosomal RNA Miseq sequencing, the proportion of phylum *Firmicutes* with SCFA production and anti-inflammatory effects was significantly reduced, whereas *Proteobacteria* were highly enriched in the AD compared with HC. In addition, similar alterations were observed at the order, class and family levels of these two phyla. The findings provided new therapeutic target for intervention or a marker for the disease.

A cohort study of dysbiosis, gut barrier dysfunction and inflammation in dementia; a pilot study

A cohort of 23 patients with dementia and 18 age matched controls without cognitive impairments was studied by Stadibauer *et al*^[21]. Gut microbiome composition, gut barrier dysfunction, bacterial translocation and inflammation were assessed from stool and serum samples. Dementia is associated with changes in gut microbiome composition and increased biomarkers of gut permeability and inflammation, *Lachnospiraceae* NKA4A136 group in *Firmicutes* was potential butyrate producer was reduced in dementia. Malnutrition and drug intake were factors that impact on microbiome composition. Increasing butyrate producing bacteria and targeting malnutrition may be promising therapeutic targets in dementia.

PROBIOTIC BIFIDOBACTERIUM BREVE A1 TO RESTORE A MILD COGNITIVE IMPAIRMENT AND DEMENTIA

In the randomized, double-blind, placebo-controlled trial by Xiao *et al*^[22], 80 healthy older adults suffering from amnesic mild cognitive impairment (a MCI) were divided into two even groups to receive once daily either probiotic *Bifidobacterium breve* A1 or placebo for 16 weeks, using a computer-generated algorithm. The results indicated that *B. breve* A1 with SCFA production, improvement of gut mucosal barrier and lower intestinal LPS levels, is a safe and effective approach for improving memory functions of suspected a MCI subjects.

EXPLORATION OF FUNCTIONAL ALTERATION OF FECAL MICROBIOTA IN CHINESE PATIENTS WITH ALZHEIMER'S DISEASE

Ling *et al*^[23] explored the alterations of the gut microbiota as well as their correlations with cognitive scores and host immunity on Chinese AD patients. The samples from 100 AD patients and 71 age-and gender-matched, cognitively normal controls were obtained to explore the structural and functional alterations of the fecal microbiota targeting the V₃-V₄ region of the 16S rRNA gene by Miseq sequencing, and to analyze their association with clinical characteristics. The data demonstrated a remarkably reduction in

the bacterial diversity and alterations in the taxonomic composition of the fecal microbiota of the AD patients. The abundant butyrate-producing genera such as *Faecalibacterium* decreased significantly, where this was positively correlated with such as clinical indications as the MMSE, WAIS, and Barthel scores in the AD patients. On the contrary, abundant lactate-producing genera, such as *Bifidobacterium*, increased prominently, and were inversely correlated with these indicators. This shift in the gut dysbiosis of the microbiota, from being butyrate producers to lactate producers, contributed to immune disturbances in the host that could be used as non-invasive biomarkers to distinguish the controls from the AD patients.

THE ASSOCIATION BETWEEN AMYLOID PATHOLOGY, BACTERIAL PRODUCTS SUCH AS LIPOPOLYSACCHARIDE (LPS) AND SHORT CHAIN FATTY ACIDS (SCFAS: ACETATE, VALERATE, BUTYRATE), INFLAMMATORY MEDIATORS, AND MARKERS OF ENDOTHELIAL DYSFUNCTION IN ALZHEIMER'S DISEASE (AD)

Marizzoni *et al*^[24] examined eighty-nine older persons with cognitive performance from normal to dementia underwent florbetapir amyloid PET (technical considerations in brain Amyloid PET imaging with ¹⁸F-Florbetapir) and blood collection. Brain amyloidosis was measured with standardized uptake value ratio versus cerebellum. Blood levels of LPS were measured by ELISA. The results showed that the amyloid-standard-uptake-value-ratio uptake was positively associated with blood LPS, acetate and valerate, pro-inflammatory cytokines, and biomarkers of endothelial dysfunction. In contrast, it was negatively correlated with butyrate and anti-inflammatory cytokine IL-10 levels. The author found a novel association between gut microbiota-related products and systemic inflammation with brain amyloidosis via endothelial dysfunction, suggesting that SCFAs and LPS represent candidate pathophysiologic links between the gut microbiota and AD pathology.

A SYSTEMATIC REVIEW AND META-ANALYSIS PERFORMED TO INVESTIGATE THE DIFFERENCES OF GUT MICROBIOTA (GM) BETWEEN PATIENTS WITH ALZHEIMER'S DISEASE (AD) SPECTRUM AND HEALTHY CONTROLS

As the data sources, PubMed, MEDLINE, Scopus, and Cochrane Library from January 2000 to August 2021 were applied by Huang *et al*^[25]. Eleven studies consisting of 378 healthy controls (HC) and 427 patients with AD spectrum were included in the meta-analysis. Patients with AD, but not cognitive impairment (MCI), showed significantly reduced GM diversity as compared to HC. The author found more abundance of *Proteobacteria*, *Bifidobacterium* and *Phascolarctobacterium*, but less abundance of *Firmicutes*, *Clostridiaceae*, *Lachnospiraceae* and *Rikenellaceae* in patients with AD spectrum as compared with HC. The inclusion of the studies is originating only from China and the US was a possible limitation. The author concluded that patients with AD spectrum demonstrated altered GM abundance, which was differentially mediated by countries and clinical stages.

The effects of probiotic supplementation on cognitive function and metabolic status

The randomized, double-blind, and controlled clinical trial was conducted by Akbari *et al.*^[26] among 60 AD patients to assess the effects of probiotic supplementation on cognitive function and metabolic status. The probiotic supplemented group took 200ml/day probiotic milk containing *Lactobacillus acidophilus*, *L. casei*, *L. fermentum* and *Bifidobacterium bifidum* for 12 weeks. After 12 weeks intervention, compared with the control group, the probiotic treated patients showed a significant improvement in the mini-mental state examination score. The author found that the probiotic treatment had no considerable effect on other biomarkers of oxidative stress and inflammation, fasting plasma glucose, and other lipid profiles. The author demonstrated that probiotic consumption for 12 weeks positively affects cognitive function and some metabolic statuses in the AD patients. Clinical Trial Registration: IRCT201511305623N60.

PUTATIVE ROLES OF ALOE INGREDIENTS IN AGING AND AGE-RELATED DISEASES

On putative prophylaxes of *Aloe vera* for age-related diseases, the check items are presented as following: prevention of cancer and alleviation of progeria, prevention of cardiovascular and cerebrovascular disorders, and preliminary clinical study of aloe-mannan multi-nutrient complex on cognitive and immune functions in AD^[27]. Aging and age-related diseases of increasing elderly population are the most challenging biomedical problem. Age-related chronic inflammatory diseases, metabolite syndrome, diabetes, kidney disease, osteoporosis, and dementia are common occurrences among the elderly. In previous review, we described putative roles of aloe ingredients and fermented butyrate based on their ability to attenuate the chronic senoinflammatory process of aging and age-related diseases^[28].

PRELIMINARY CLINICAL STUDY OF AN ALOE-MANNAN MULTI-NUTRIENT COMPLEX (AMC) ON COGNITIVE AND IMMUNE FUNCTIONING IN AD

AMC formula used by Lewis *et al.*^[29] showed a significant improvement in the AD assessment scale-cognitive score and demonstrated sound immune modulator activity with noteworthy responses in cytokines and several lymphocytes and monocyte subsets. The results showed that a high quality, concentrated dietary supplement may offer an alternative option for persons with AD. The AMC formula may not only facilitate cognitive improvement, but may also improve the inflammatory and immune function profile as well, thereby enhancing host recovery and improving overall QOL.

CASE REPORTS

In three case reports of the previous paper we described that Kampo medicine, Yokukansan, that is tolerated and effective remedy that improves the symptoms of schizophrenia and behavioral and psychological symptoms of dementia, with aloe vera juice (AVJ)-adjuvant, exhibited a possible efficacy to brain homeostasis^[30]. AVJ supplementation by producing butyric acid may support the therapy with Kampo medicine and provide an important play in the modulation of brain homeostasis.

Case report 1

A ~seventy three-year old female who was obese with hypertensive and diabetic symptoms, was needed nursing care level 2. She was administered hypotensive, antianginal, antidiabetic and cognition enhancer drugs on July 2021. Then she ingested aloe vera juice (AVJ) with hypotensive, antianginal, antidiabetic and cognition enhancer drugs. After three month's ingestion of AVJ with the hypotensive (Azilsartan tablets), hypoglycemic (Vildagliptin tablets), antianginal (Nifedipine), and cognition enhancer (Memantine hydrochloride) drugs, the blood examination on blood pressure and glucose level showed normalized level and surprisingly, the nursing care level 2 mitigated into level 1. Since then, she ingested daily AVJ with above mentioned drugs and multivitamin and she has well-being QOL in nursing care level 1 on April, 2022.

CONCLUSION

Short chain fatty acid, butyric acid, not only signals through binding to cognate G-protein-coupled receptors on endocrine and immune cells in the body, but also induces epigenetic changes in the genome through effects on the activity of histone acetylase and histone deacetylase enzymes^[31]. Butyrate was shown as one of the main players in the interplay between diet, microbiota, and health conditioning such as Alzheimer's disease and dementia progression.

In case report 1, the hypotensive, antianginal, hypoglycemic and cognition enhancer drugs in a frail female obese patient who was needed in nursing care level 2, moderated into the nursing care level 1 through the daily ingestion of AVJ with above mentioned drugs and multivitamin. The efficacy of the drugs in a frail female patient needed the nursing care level 2, may be supported with daily ingestion of aloe vera juice, the drug and multivitamin modulating from the nursing care level 2 into 1 and providing an important role in the modulation of brain homeostasis.

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