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Case Report

The Role of Butyrate Fermented in Aloe Vera Gel to Neurological Dysfunction in Post-acute COVID-19

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Abstract

COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestation. COVID-19 survivors have described prolonged malaise, diffuse myalgia, depressed symptoms, and non-restorative sleep as a post-viral syndrome. In this study, we looked at how butyrate fermented in aloe vera gel helped post-acute COVID-19 patients with neuropsychiatric symptoms such sadness, anxiety, and sleeplessness. The adjuvanticity of aloe vera gel to COVID-19 vaccination and the mitigation of side effects from Covid-19 immunisation after surgery were demonstrated in case studies.

Keywords: *Fermented Butyrate; Aloe Vera Gel; Neurological Dysfunction*

Introduction

Plant-based, high-fiber diets are a good source of microbiota-accessible carbohydrates, which promote intestinal health by creating short-chain fatty acids and give a variety of health advantages to the host, including improved immunity. As a result, a precisely tailored diet can aid in the recovery and therapeutic results of COVID-19 patients [1]. Following infection with COVID-19, it has been observed that the gut microbiome is changed and classified as dysbiotic. Finally, a reduction in the quantity of particular *Lactobacillus* and *Bifidobacterium* species is frequently achieved. In view of the urgent need to cure and rehabilitate a large percentage of the population in the post-COVID-19 period, the gut microbiota is very crucial. Despite the fact that COVID-19 is largely a respiratory infection, there is growing evidence that the gut microbiota is implicated in the disease. In a pilot study of 15 patients with COVID-19, Zuo., *et al.* [2] discovered continuing alterations in the fecal microbiome during the time of hospitalization, compared with controls. Fecal microbiota alterations were associated with fecal levels of SARS-Cov-2 and COVID-19 severity. Strategies to alter the intestinal microbiota might be reduced disease severity. Yeoh., *et al.* [3] investigated whether the gut microbiome is linked to disease severity in patients with COVID-19 in the hospital cohort study in China. Several gut commensals with known immunomodulatory potential such as butyrogenic bacteria (butyrate-producing bacteria); *Faecalibacterium* and *Bifidobacteria* were underrepresented in patients and remained low in samples collected up to 30 days after disease resolution. The abundance butyrate-producing bacteria, such as *F. prausnitzii*, *Clostridium butyricum, C. leptum*, and *Eubacterium rectale*, decreased significantly, and this shift in bacterial community may help differentiate critical patients from general and severe patients [4]. In patients with COVID-19, associations between gut microbiota composition, cytokine levels, and inflammatory markers revealed that the gut microbiome is implicated in the severity of COVID-19 by influencing host immune responses. The function of the gut microbiota during respiratory viral infections was discussed in our earlier study [5], and it was hypothesised that treating gut dysbiosis with aloe vera gel could help control the immunomodulatory influence on COVID-19 pathogenesis. And aloe vera juice use for seven years enhanced the comparative faecal level of butyrogenic prebiotic *Faecalibacterium* spp. by 3.4 percent in a 61-year-old female [6,7].

The significance of butyrate fermented in aloe vera gel and human gut microbiota in post-acute COVID-19 and neuropsychiatric sequelae is discussed in this paper. In case reports, vaccinated people experienced a high-quality of life (QOL) after ingesting aloe vera juice (AVJ), and there was evidence of AVJ adjuvanticity after surgery.

The relationship between gut microbial metabolites and brain

Several metabolites have a role in the connection between the gastrointestinal tract and the central nervous system, and they have the ability to influence physiological and pathological processes in the brain. The biochemical interaction can take place in a variety of ways, both direct and indirect.

Binding to host receptors in the brain, activation of the vagus nerve in the gut, changes in central neurotransmission, and modulation of neuroinflammation are just a few examples. Short chain fatty acids, bile acids, neurotransmitters, and other bioactive microbiome products have been shown to play an important role in the gut-brain axis, according to Caspani and Swanne [8]. One of the most exciting areas in microbiome research is the link between gut microbial metabolism and mental health. Valles-Colomer., *et al.* [9] investigated the relationship between microbiome characteristics and host quality of life and depression. Bacteria that produce butyrate, such as *Faecalibacterium* and *Coprococcus*, were consistently linked to greater quality of life indicators. The results provided population-scale evidence for microbiome links to mental health, emphasizing note-worthy importance.

The epigenetic regulation of microglial activation by histone deacetylase inhibitors

Understanding regulation of microglia activation will aid in the development of therapeutic strategies that mitigate microglia-mediated neurotoxicity in neuro-pathologies, including ischemia. Patnala., *et al*. [10] examined the epigenetic regulation of microglia activation by studying histone 3-lysine 9-acetylation (H3K9ac) and its regulation by histone deacetylase (HDAC) inhibitors. The *in vitro* analysis of activated microglia showed that HDAC inhibitor, sodium butyrate (SB) alters H3K9ac enrichment and transcription at the promoters of pro-inflammatory and anti-inflammatory (IL-10) genes. A similar upregulation of H3K9ac was detected in lipopolysaccharide-activated microglia in the Wister rat brain, indicating that H3K9ac upregulation is consistently associated with microglial activation *in vivo*. Evidence of HDAC inhibition was found to represent a promising molecular switch for epigenetically changing microglial activity from pro-inflammatory to anti-inflammatory, potentially reducing microglia-mediated neuroinflammation. Van de Wouw., *et al.* [11] provided new insights into the processes behind the gut microbiota's influence on brain homeostasis, behavior, and host metabolism, paving the way for the development of microbiota-targeted stress-related diseases therapeutics. In male mice, treatment with short chain fatty acids (SCFAs) reduced psychosocial stress-induced changes in reward-seeking behavior and increased response to an acute stressor as well as *in vivo* intestinal permeability. Furthermore, SCFA produced antidepressant and anxiolytic effects in behavioral tests that were not apparent when mice had also been exposed to psychosocial stress. SCFA supplementation alleviates selective and long-lasting changes caused by recurrent psychosocial stress, according to the findings.

Short chain fatty acid deficiency and disturbance of gut-microbiota-brain axis signaling in COVID-19 patients

In neurological illnesses, the gut-brain axis demonstrates a bidirectional flow of interactions between the brain and gut bacteria. COVID-19 severity may be exacerbated by lifestyle factors.

Batty., *et al.* [12] looked into the link between a variety of psychosocial characteristics and COVID-19 hospitalization. In the analytical sample of 431,051 England-based research participants, there were 908 COVID-19 hospitalizations. A variety of psychosocial characteristics were shown to be associated with COVID-19 hospitalization, with the relationship with cognitive function, a measure of health literacy, being the strongest. COVID-19 may generate stress, which in turn increases the severity of COVID-19, creating a feedback loop. As a result, lifestyle stressors could be a major risk factor for COVID-19.

The relationship between COVID-19 and neuropsychiatric illnesses must be understood as soon as possible. The number of COVID-19-related neuropsychiatric problems is on the rise. Sajdel-Sulkowska [13] demonstrated that SARS-CoV-2 infection causes gut dysbiosis and an altered microbiota-gut-brain (MGB) axis, which contributes to COVID-19's neuropsychiatric effects. Changes in MGB axis activity have been linked to a higher incidence of neuropsychiatric diseases.

Notably, the number of bacteria that produce short chain fatty acids (SCFA) decreased. SCFA are anti-inflammatory bioactive microbial metabolites that have been identified as a major signaling mechanism in the MGB axis.

Gut microbiota interaction with the central nervous system

Microbiota-gut-brain axis in depression

A growing body of research suggests that the gut microbiota may have a role in the pathophysiology of depression. In depressed mice, Wu., *et al.* [14] investigated the link between alterations in neurotransmitters and short chain fatty acids (SCFAs) and changed gut flora. The chronic restraint stress model of depression was used by the author. Between depressed animals and control mice, twenty-nine distinct bacterium taxa were discovered. Depressed mice had lower levels of SCFAs, norepinephrine, 5-hydroxyindol acetic acid, and 5-hydroxytryptamine than control mice. The findings provided new microbiological and metabolic frameworks for comprehending the microbiota-gut-brain axis' function in depression.

Sodium butyrate (NB), a histone deacetylase inhibitor, shows antidepressant-like effect in preclinical studies: the exact mechanisms

Wei., *et al.* [15] indicated that sodium butyrate (NB), having a histone deacetylase inhibitor (HDACi), has also evidence that NB affects DNA methylation. The author looked at the effects of NB on DNA methylation alterations in the prefrontal cortex of an established genetic rat model of depression (the Flinders Sensitive Line (FSL)) and its control (the Flinders Resistant Line).

Ten-eleven translocation methylcytosine dioxygenase 1 (TET1), which catalyses the conversion of DNA methylation to hydroxymethylation, was shown to be reduced in FSL rats. Chronic treatment of NB had antidepressant-like effects in the FSL, as indicated by the behavioural despair test, and was associated by elevated levels of TET1. TET1 overexpression was also linked to an increase in hydroxymethylation and a decrease in methylation in brain-derived neurotrophic factor (BDNF), a gene linked to synaptic plasticity and neurogenesis. These epigenetic modifications were linked to an increase in the expression of BDNF. The author determined the antidepressant efficacy of HDACis and suggested that their epigenetic effects may also include DNA methylation changes that are mediated by demethylation-facilitating enzyme like TET1.

The mechanism of NB's antidepressant effects was demonstrated by the author. Several preclinical studies demonstrating the antidepressant-like effects of HDAC inhibitors were reviewed by Fuchikami., *et al*. [16], and the idea of employing HDAC inhibitors in patients with treatment-resistant depression was considered. Chronic stress has been shown to cause long-term genomic changes (such as histone modifications and DNA methylation) that may contribute to the aetiology of depression. The findings revealed that an individual's reaction to environmental cues, stress, and even antidepressant therapies is shaped by epigenetic control of the BDNF gene.

The role of short chain fatty acids to the patients with neurodevelopmental disorders

Bojovic., *et al.* studied the gut microbiota diversity and composition in 36 children diagnosed with neurodevelopmental disorders (NDD) and 28 healthy children from the Republic of Serbia [17].

In comparison to the control group, the NDD patient group had a higher incidence of potentially dangerous bacteria closely linked to Clostridium species. The NDD group of patients, on the other hand, had a much-decreased diversity of common commensal microorgan-

isms. Furthermore, the butyrate-producing bacteria *Faecalibacterium prausnitzii* and *Butyricicoccus pullicaecorum* were found in lower numbers in the NDD patients. The amounts of faecal short chain fatty acids (SCFAs) were measured in accordance with this. Although no significant differences in SCFA levels were found between NDD patients and the control group, there was a positive correlation between the number of rDNA amplicons obtained with universal primers and the level of propionic acid in the control group, as well as a trend for total SCFAs and butyric acid. The gut microbiome of NDD patients differs from that of healthy youngsters, according to the study. The early life microbiome may play a role in the gastrointestinal disorders and behavioural difficulties that are common in patients with a wide range of NDD.

Microbiota-gut-brain axis in chronic pain and depression

The gut microbiota appears to have a crucial role in the aetiology of neurodevelopmental and neurodegenerative illnesses via the gut-brain axis, according to mounting data. Different communication channels between the gut bacteria and neuronal tissues have been elucidated by recent study (e.g., the vagus nerve, tryptophan production, extrinsic enteric-associated neurons, and short chain fatty acids). Ojeda., *et al*. [18] compiled a summary of recent data on the impact of the gut microbiome on the start and progression of neurodevelopmental and degenerative illnesses. The author discussed ways for modulating composition in the search for therapeutic options, with a particular emphasis on animal model studies. In clinical practise, chronic pain is usually associated with depression. Alterations in gut microbiota and metabolites derived from it have recently been discovered to play a role in aberrant behaviours and cognitive impairment via the microbiota-gut-brain axis. Before October 1, 2019, Li., *et al*. [19] searched PubMed for relevant papers concentrating on "the latest evidence of gut microbiota and metabolites in chronic pain and depression in animal and human research." Changes in gut microbiota and their metabolites have been shown to affect neuro-inflammation and neuro-immunity in the onset and transmission of pain and depression in both animal and human studies. The findings suggested that dysbiota dysbiosis may play a role in the development and treatment of chronic pain and depression. The bacteria-derived metabolites, such as SCFAs, tryptophan-derived metabolites, and secondary bile acids, provided new insight into the potential relationship between gut microbiota triggers and depression processes.

Protective effect of sodium butyrate against Parkinson's disease in mice and case reports

The inflammatory responses in different neural inflammation models in cell cultures were studied by Huuskonen., *et al*. [20]. Butyrate treatment in transformed N9 cells and in hippocampal slice cultures downregulates the NF-κB-binding capacity induced by LPS stimulation. The results showed that butyrate is anti-inflammatory in primary, brain-derived microbial cells.

Sodium butyrate (NaB) has exhibited protective activity in neurological disorders. Liu., *et al*. [21] investigated the neuroprotective effect and potential mechanisms of NaB in a mouse model of Parkinson's disease (PD). A mouse was intraperitoneally treated with 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine hydrochloride (MPTP) for 7 consecutive days to induced PD model. To the treated mouse model of PD, NaB (200mg/kg) was intra-gastrically treated with for 3 weeks. The results showed that NaB improved neurobehavioral impairment including cognitive behavior and coordination performance. Particularly, NaB-treated mice with PD exhibited increased colonic glucagon-like peptide-1 (GLP-1) level as well as upregulation of brain receptor expression compared with PD group. Thus the findings suggested NaB has potential as a novel therapeutic for treatment of PD, and its mechanism was associated with stimulating colonic GLP-1 secretion.

Prophylactic role of aloe supplementation on patients with Parkinson's disease

In preliminary case report [22] we reported that treatment of Parkinson's disease (PD) drug with aloe vera supplementation (aloe vera juice (AVJ) +ω-3PUFA and L-Arginine) improves cognition and muscle stretching. For instance the PD patients with diabetes at stage 3 were in remission PD-stage 2 by treatment of PD-drug with aloe supplementation after several month treatments. The patients at PD-stage 3 were in remission PD-stage 0 by the treatment of PD-drug with aloe supplementation after two months. The two case reports suggested that the efficacy of nutraceutical aloe supplementation was fully expected for risk factors in PD patients with/without diabetes.

In additional case report, the ingestion of AVJ for seven-years in 61-years old frail female increased 3.4 hold higher in the comparative fecal content of butyrogenic probiotic *Faecalibacterium* spp. It is suggested that the PD-associated microbiota may harbor microbes and functions that drive this neurodegenerative disease.

Modified Mediterranean-ketogenic Diet modulates gut microbiome

The gut microbiota may have a role in Alzheimer's pathogenesis and may aid in the discovery of new markers and treatments for the disease (AD). Nagpal., *et al*. [23] evaluated if and how a modified Mediterranean-ketogenic diet (MMKD) alters the gut microbiota profile in relation with cerebrospinal fluid (CSF) AD indicators in older persons with moderate cognitive impairment compared to cognitively normal counterparts. For 6-weeks, 17 patients are randomised, double-blind cross-over, single-center pilot study of MMKD against American Heart Association Diet (AHAD) intervention, 11 of whom have mild cognitive impairment and 6 of whom are cognitively normal. In participants with mild cognitive impairment, proteobacteria linked favourably with Abeta -42, Abeta -40, while faecal propionate and butyrate correlated negatively with Abeta -42. The two diets have varied effects on different microorganisms, with diverse patterns in cognitively normal and impaired patients. On MMKD, the quantity of Enteobacteriaceae, Akkermansia, Slackia, Christensenelliaceae, and Erysipelotriaceae increased, whereas *Bifidobacterium* and Lactnobacterium decreased, and Mollicutes increased. Fecal lactate and acetate are modestly reduced by MMKD, but propionate and butyrate are increased. AHAD, on the other hand, raises acetate and propionate while lowering butyrate.

Identification of Faecalibacterium prausnitzii strains linking the gut-brain axis to Alzheimer's disease

Evidence linking the gut-brain axis to Alzheimer's disease (AD) is accumulating. Ling., *et al*. [24] explored the structural and functional alteration of the fecal microbiota targeting the V3-V4 region of the 16S RNA gene by MiSeq sequencing and analyzed their diversity and alterations in the taxonomic composition of the fecal microbiota of the Chinese Parkinson's disease patients. The data demonstrated a remarkable reduction in the bacterial diversity and alterations in the taxonomic composition of the fecal microbiota of AD patients. The abundance butyrate-producing genera such as *Faecalibacterium* decreased significantly, where this was positively correlated with such as clinical indicators 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 results suggest the potential for use of gut bacteria for the early, non-invasive diagnosis of AD, personalized treatment, and the development of tailor-made probiotics designed for Chinese AD patients. Ueda., *et al*. [25] examined a fecal microbiome analysis in healthy subjects and those with mild cognitive impairment (MCI) and AD. The author found that *F. prausnitzii* correlates with cognitive scores and decreased in the MCI group compared with the healthy group. Two isolated strains from the healthy group, live Fp360 and pasteurized Fp14, improve cognitive impairment in an AD mouse model. The author concluded that *F. prausnitzii* strains with specific orthologs are candidates for gut microbiome-based intervention in AD-type dementia.

Gut-brain communication: Silent hypoxia in COVID-19

Gopal., *et al*. studied the gut-brain connection during hypoxia in uninfected and SARS-CoV-2-infected non-dyspneic hypoxic people [26]. The author demonstrated that SARS-CoV-2-induced gut dysbiosis alters the production of short chain fatty acids (SCFA) and other metabolites, as well as causing inflammation and blood-brain barrier disruption. As a result, viral participants, elevated inflammatory mediators, reactive oxygen species, neurotropic gut microbial metabolites, and reduced SCFA can harm central and peripheral hypoxia detecting neurons in infected patients.

In COVID-19, neuromodulators from a dysbiotic gut may impact the central nervous system and carotid body, resulting in silent hypoxia.

Prevention of sodium butyrate to memory impairment

Pneumococcal meningitis is a serious infection of the central nervous system with high fatality rats that causes reduced psychomotor performance, slight mental slowness, impairment in attention executive function and learning and memory deficiencies. Barichello., *et al*. [27] investigated that a correlation between memory impairment and decreased levels of brain-derived neurotrophic factor (BDNF) in the hippocampi of rats subjected to pneumococcal meningitis. Emerging evidence demonstrates that histone acetylation regulates neurotrophins; therefore, a potential molecular intervention against cognitive impairment in bacterial meningitis may be the histone deacetylase inhibitor, sodium butyrate, which stimulates the acetylation of histones and increases BDNF expression. In animal study, rats received either artificial cerebrospinal fluid as a placebo or a Streptococcus pneumoniae suspension. The rats received antibiotic treatment as usual and received saline or sodium butyrate as an adjuvant treatment. Ten days after, meningitis was induced, and their hippocampi were removed to evaluate the expression of BDNF, nerve growth factor and glial cell line-derived neurotrophic factor (GDNF). In the meningitis group that received saline, the rats presented memory impairment in both behavioral tasks, and hippocampal BDNF and GDNF expression was decreased. Sodium butyrate was able to prevent memory impairment and re-establish hippocampal neurotrophins expression in experimental pneumococcal meningitis.

The effect of butyrate reversing obesity-induced social deficits and anxiety-like behaviors via regulation of mice-microglia homeostasis

High-fat diet (HFD) mice that are administered *Lactobacillus reuteri* are found to accumulate butyrate in their gut, sera and brain by Duan., *et al*. [28]. Supplementation of butyrate improves behavioral abnormalities and modulates microbial homeostasis in HFD-mice. Selectively removal of microglia through a pharmacologic approach can rescue dendritic spine loss and increase neuronal activity that profoundly alleviates social deficits and anxiety arising from HFD-induced obesity. The author revealed an unexpected pivotal role of gut commensal-derived butyrate in HFD-induced social deficits and anxiety-like behaviors through regulation of microglial homeostasis and identifies a potential probiotic treatment for HFD-induced obesity-related bacterial abnormalities.

A cohort study on post-COVID-19 syndrome

At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severe ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations and are the main target population to intervention of long-term recovery. Huang., *et al*. [29] deeply searched an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital between Jan 7, 2020, and May 29, 2020. Fatigue or muscle weakness and sleep difficulties were the most common symptoms. Anxiety or depression was reported among 23% of patients.

Intestinally produced butyrate may serve as a bacterial-derived sleep-promoting signal

Bacterial metabolites and components of the bacterial cell wall are likely to provide important links between the intestinal commensal flora and sleep-generating mechanisms in the brain. Szentirmai., *et al*. [30] investigated the effects of oral administration, direct intraportal injection, as well as systemic injection of butyrate in mice and rats. The results demonstrated that oral and intra-portal administration of butyrate induced robust increase in non-rapid-eye movement sleep, while systemic butyrate treatment has no effect on sleep. The findings indicated the existence of a butyrate-sensitive hepatic portal sleep-inducing sensory mechanism.

A microbiome-driven approach to rebalance the depression during the COVID-19 pandemic

On a relationship between depression and the microbiome, the given association of COVID-19 with stress and depression, Ghannoum., *et al*. [31] proposed that one approach to combat depression should include potential diet modification, nutritional supplements and life-

style changes. Specially, increasing the abundance of beneficial organisms that exhibit a reduction in their levels during stress and depression (e.g., *Faecalibacterium*, *Bifidobacterium,* and *Lactobacillus*) and decrease the levels of pathogens, such as Candida, Corynebacterium and Ruthenbacterum, should supply an improved gut microbiome.

Studies on COVID-19 symptoms and gut health in Lebanese patients

Al Kassaa., *et al*. [32] demonstrated a potential association between gut health and COVID-19 severity in the Lebanese community. The author investigated the cross-sectional study of SARS-CoV-2 PCR-positive Lebanese patients. Participants were interviewed and gut health, COVID-19 symptoms, and different metrics were analyzed using simple and multiple logistic regression models. The results manifested the impact of gut health and exposure to respiratory viruses on COVID-19 severity and the smoothly facility to combat against the pandemic in Lebanon.

Neuropsychiatric sequelae in post-acute COVID-19 syndrome

Nalbandian., *et al*. [33] provided a comprehensive review of the current literature on post-acute COVID-19, its pathophysiology and its organ-specific sequelae, and discussed relevant considerations for the multidisciplinary care of COVID-19 survivors and proposed a frame work for the identification of the multiple-disciplinary care of COVID-19 survivors at high risk for post-acute COVID-19 and their coordinated management through dedicated COVID-19 clinics. The author recommended the standard therapies should be implemented for neurologic complications such a headache, with imaging evaluation and referral to a specialist reserved for refractory headache.

Case Reports

Case Report 1: Mitigation of side effects with aloe vera juice (AVJ) ingestion of ~40 years-old female who had two-times vaccination of COVID-19: Comparison between AVJ ingestion and no-ingestion subjects

In case of five subjects who are ingesting AVJ every day, they had a weak pain in the injection site, but no fever. On the other hand, in case of five subjects who had no AVJ ingestion, one for five subjects had fever for one day and four for five subjects had fever for 2-3 days. Besides, five-no AVJ ingestion subjects continued to have a strong pain in the injected site of vaccination and muscular pains around the arm for several days.

Case Report 2: AVJ ingestion-efficacy in the prognosis of the aorta dissociation surgery after two-times vaccination of COVID-19

A ~70-year-old female had a severe strangling pain around neck and breast after vaccination and she immediately ingested AVJ 400ml. Then she became calm after one hour. She examined an electrocardiogram in the hospital on October 26, 2021 but had no heart-trouble. She continued to have her heart trouble with hypotensive of blood pressure (65/53 mmHg). She had injected COVID-19 vaccination two times on the middle of September and October and was suspected of thrombus. She administered Kampo blood stasis medicine: Ketsupuchikuo-to with AVJ to November 1, 2021. She had a severe pain in the back on November 6, 2021. Immediately she entered the hospital and was diagnosed the main aortic dissection and she was instantly operated. After the operation she ingested AVJ 1000ml/day and since then, she had a well QOL to December 1, 2021. The surgical doctor noticed that AVJ ingestion may play a beneficial role for regression after the surgery.

Case Repot 3: Mitigation of side effects from two-times vaccination for COVID-19 with AVJ ingestion in ~70-years old male

The triathlon-lover subject who had training such as swimming and running every days, could not move and stretch his arms from vaccination for COVID-19 on May, 2021, because of the fever, muscle strain, and languid-feeling. After one week he got back to normal temperature, but he still could not normally walk and move. He was diagnosed as an early stage of spinal canal stenosis. Since then he

started ingestion of AVJ 100ml/day and he had a well QOL after ingestion of AVJ for 6 months and he can practice a mild exercise on November, 2021.

Discussion of Case Reports

Aloe vera gel has been demonstrated to have immunomodulatory properties and is safe to consume.

[34]. Acemannan, an immune stimulant and adjuvant derived from aloe vera gel, was considered as an immune stimulant and adjuvant for human immunodeficiency virus infection, as well as the role of food and host-microbial cross talk in maintaining homeostasis [35]. In case reports 1 and 3, aloe vera gel juice was used as an adjuvanticity to COVID-19 vaccination, while in case report 2, Kampo blood stasis medicine with aloe vera gel was used as an adjuvanticity to COVID-19 vaccination after surgery. The benefits of AVJ intake for COVID-19 vaccination-related adverse effects have been documented.

Conclusion

Faecalibacterium prausnitzii, a butyrate-producing anaerobe normally linked with excellent health, has been found to be inversely related to disease severity in COVID-19 gastrointestinal sequelae. *F. prausnitzii* may have the capacity to minimise microbial translocation and inflammation, reducing gastrointestinal comorbidities in COVID-19 patients. The gut microbiota is particularly relevant in the post-COVID-19 period, given the urgent need to treat and rehabilitate a large segment of the population. A microbiome-based holistic approach, which include carefully documenting the microbiome and possible modification by diet, probiotics, and lifestyle modifications, could help those with depression.

Global advances in the study of the human microbiome, butyrate-producing microbiota, and dietary butyrogenic supplements like aloe vera juice [6,7] and the Mediterranean-ketogenic diet [23], have opened up new horizons in personalised medicine for neurology dysfunction in post-acute COVID-19 syndrome. Beneficial metabolites like as short chain fatty acids and butyrate may be lacking in COVID-19 due to dysbiosis. It has been claimed that butyrate, which is produced in the stomach and fermented in aloe vera gel, can be used to reduce the severity of COVID-19 infections. The adjuvanticity of AVJ intake following COVID-19 vaccination was clearly demonstrated in case reports 1 and 3.

Furthermore, in case report 2, Kampo blood stasis medicine combined with aloe vera gel adjuvanticity may have contributed to the improved prognosis following surgery.

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