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Review Article

Possible Prophylaxes of *Aloe vera* Gel and *A. arborescens* Fermented Butyrate on Insulin Sensitivity, Extracellular Signal-Regulated Kinase Signaling and ß-Secretase Inhibition for Elder Alzheimer's Dementia Subjects Case Report: Restoration from Parkinson's Dementia with the Drug and *Aloe vera* Juice Ingestion

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Abstract

Case report 1: A ~80-years old female who was diagnosed as Parkinson's disease (PD), had such as symptoms; slowed movement, speech changes, non-reading news-paper and no self-reliance excretion, started to take the administered drugs, and ingested *Aloe vera* juice (50 ml/day) and supplements on 2017. Since then, she significantly improved her PD-dementia symptoms, and reading the newspaper without any suggestion with family. Finally, she is well-being QOL, although PD can't be cured perfectly on May, 2023.

Keywords: *Parkinson's Disease (PD); A. arborescens; ß-Secretase; Alzheimer's Dementia; Parkinson's Dementia*

Introduction

Insulin is a key hormone regulating metabolism and the disturbances in metabolic health can increase the risk of developing Alzheimer's dementia. Since insulin has a key role in learning and memory as well as directly regulating extracellular signal-regulated kinase (ERK), a kinase required for the type of learning and memory compromised in early Alzheimer's disease (AD), insulin resistance has been identified as a major risk factor for the onset of AD by Dineley., *et al* [1]. Based on recent inquiries to Clinical trials, gov., Lee., *et al*. [2] evaluated thirty-three clinical studies related to AD and insulin. The search filtered for interventional clinical trials to test FDA-approved

drugs or substances that impinge upon the insulin signaling pathway. Insulin, metformin, and thiazolidinediones were the three main interventions assessed. The strategy is expected to negate the effects of brain insulin resistance by targeting insulin signaling pathways involved in neuroinflammation and metabolic homeostasis. In a previous report, it was suggested that *Aloe vera* protects metabolic health and affects insulin levels, impairs blood flow to the brain and impairs memory [3].

Present review describes the effect of dietary supplementation of fermented butyrate in *Aloe vera* and *Aloe arborescens* on brain-derived neurotrophic factor and immune-modulatory functions in elderly subjects with Alzheimer's dementia. Butyric acid cycle with *Aloe vera* and *A. arborescens* about human immune-modulation was positively discussed. In case report 1, the patient with Parkinson's dementia was treated with the administration drugs, *Aloe vera* juice (AVJ), and aloe supplements in 2017. Although she can't be cure Parkinson's dementia perfectly, she is well-being with AVJ and aloe supplements, and a nice QOL in May, 2023.

ß-secretase inhibitory chromone glycosides from *Aloe vera*

ß-secretase (BACE1) is one of the enzymes that contribute to the formation of Alzheimer's ß (Aß) plaques; Aß (1-42) which lead to dementia. Lv., *et al*. [4] isolated four chromone glycosides from *Aloe* spp. plants; *A vera* and *A. nobilis*. The preliminary structure-activity relationship of aloe chromone glycosides were discussed. *Aloe vera* contains active compounds that are natural BACE1 inhibitors and can aid in the inhibition of ß-secretase enzyme and thus BACE1 inhibitory from *A. vera* and *A. nobilis* could protect brain health and prevent AD.

Active constituents from Aloe arborescens as BACE inhibitors

Gao., *et al*. [5] isolated BACE-moderate inhibitors identified as aloenin A, (E)-2-acetonyl-8-(2'-O-feruloyl)-ß-D-glucopyranosyl-7-methoxy-5-methyl-chromone, 7-O-methylaloeresin A, and barbaloin A from *Aloe arborescens*.

Aloe arborescens extract protect IMR-32, a neuroblastoma human cellular line, from toxicity induced by ß-amyloid

Clementi., *et al*. [6] provided evidence that Aloe arborescens extract protects IMR-32, a neuroblastoma human cellular line, from toxicity induced ß-amyloid, the peptide responsible for Alzheimer's disease. In particular, pretreatment with *A. arborescens* extract maintains an elevated cell viability and exerts a protective effect on mitochondrial functionality, as evidenced by oxygen consumption experiments. The protective mechanism exerted by *A. arborescens* seems to be related to lowering oxidative potential of the cells, as demonstrated by the ROS measurement compared with the results obtained in the presence of amyloid ß (1-42) peptide alone. Based on these preliminary observations the author suggested that use of *A. arborescens* extract could be developed as agents for the management of Alzheimer's disease.

Decreased in barbaloin and product of butyric acid fermented by endophytic bacteria in *Aloe arborescens* leaves

In preliminary investigation of the endophytic fermentation of *Aloe arborescens*, we found that decrease in barbaloin and production of short chain fatty acids; acetic, propionic and butyric acid were identified by GC/MS analysis. Reduction of barbaloin concentration was found to be 14ppm by HPLC analysis. Dietary intake of the fermented extract by endophytic microbiota in *A. arborescens* leaves provided beneficial influences to human health maintenance of homeostasis [7].

Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) as a biological candidate marker of Alzheimer's disease (AD)

Alzheimer's disease (AD) is characterized by the progressive formation of insoluble amyloid plaques and vascular deposits consisting of the amyloid ß-peptide (Abeta) in the brain. Pathological mechanisms are already active early in the pre-symptomatic stage of AD. BACE1, ß-secretase, is one of the two key enzymes in amyloid precursor protein (APP) processing; the other being γ-secretase. The

Abeta peptide results from cleavage of APP initially by BACE1 to produce the C99 fragment and releases soluble APPbeta; C99 is then further cleaved by γ-secretase leading to the Abeta peptide. Increased BACE1 activity and elevated levels of insoluble Aß peptide have been shown in brain tissue of patients with sporadic AD. BACE1 activity was significantly correlated with BACE1 protein concentration and total Abeta levels. Hampel., *et al*. [8] reviewed the current studies ongoing to validate BACE1 and functionally associated proteins as candidate biomarkers for early detection, prediction, progression as well as for biological activity in AD.

The effects of *Aloe vera* extract on mitochondria rat pheochromocytoma cells（PC12）and rat brain and to study the mechanism of its neuroprotection

Aloe vera extract could improve mitochondrial damage induced by sodium azide in PC12 cells.

And it also protected the structure and function of mitochondria in rat brains. Wang., *et al*. [9] investigated the protective effects of *Aloe vera* extract on mitochondrial cells and rat brain.

The effect of aloe polysaccharide (AP) pretreatment on the cerebral inflammatory response and lipid peroxidation in severe hemorrhagic shock rats first entering high altitude

Lu., *et al*. [10] investigated 40 healthy male rats divided into 5 groups; sham group, shock group, AP group was further divided into 3 subgroups (AP1,0.75mg/kg; AP2 1.5mg/kg; AP3 300mg/kg). The different doses AP were given iv respectively at 30 min before hemorrhagic shock. Compared with the sham group, hemorrhagic shock significantly increased serum TNF-α, IL-6 and IL-10 concentrations, MPO activity and MDA concentration in the brain tissue and brain W/D, while SOD activity decreased significantly compared to the shock group. There was no significant difference between AP2 and AP3 groups. In conclusion, AP pretreatment can attenuate the cerebral ischemia and reperfusion injury in severe traumatic-hemorrhagic rats first entering high altitude through inhibiting systemic inflammatory response and leukocyte aggregation and lipid peroxidation in the brain.

Preliminary clinical study of an Aloe-mannan multi-nutrient complex (AMC) on cognitive and immune function in Alzheimer's disease

AMC formula used by Lewis., *et al*. [11] showed a significant improvement in the AD assessment scale-cognitive score and demonstrated sound immune modulator activity with noteworthy response in cytokines and several lymphocytes and monocyte subsets. The AMC formula may not only facilitate cognitive improvement, but also improve the inflammatory and immune function profile as well, thereby enhancing host recovery and improving overall QOL.

The effect of an Aloe polymannose multinutrient complex (APMC) on pro-brain-derived neurotrophic factor (BDNF) and mature BDNF in persons with moderate to severe Alzheimer's dementia

A 12-month open-label trial was utilized to evaluate the effect of the APMC on pro-BDNF and BDNF and their relationship to cognitive functioning by Martin., *et al* [12]. Thirty-four adults were enrolled and consumed 4 teaspoons/day of APMC for 12 months. Subjects were assessed at baseline and twelve months follow-up for pro-BDNF and BDNF and with a neuropsychological battery to measure cognitive functioning. The author found that the relationship between cognitive functioning and BDNF and BDNF//proBDNF ratio improved in response to consumption of a dietary supplement in persons with Alzheimer's dementia, which is consistent with the previous findings on cognitive functioning. The obtained results showed modest improvements in clinical outcomes for a disease that otherwise has no standard conventional approach to treatment with proven efficacy.

The relationship among pro-brain-derived neurotrophic factor (BDNF) and immune functioning during Aloe polymannose multinutrient complex (APMC) treatment in person with moderate to severe Alzheimer's dementia (AD)

An open-label trial of 12 months was used to execute the study by Stillman., *et al* [13]. Thirty-four adults with AD were enrolled and consumed four teaspoons/day of APMC for 12 months. Subjects were assessed at baseline and 12 months follow-up for pro-BDNF and BDNF and cytokines, growth factors, T-cell and ß-cell subsets, and complete blood count to measure immune functioning. All biomarkers were intercorrelated. The associations between BDNF and proBDNF and various immune markers, such as VEGF, EGF, and CD95+/CD3+ratio, provide insight into the link between neurological function and the immune system. These relationships were even stronger in response to APMC treatment, which lends support to previous findings showing improved immune function after dietary supplementation. The use of the dietary supplement of APMC may benefit these patients by simultaneously improving immune and neurological function.

Association of butyrate fermented in *Aloe vera* gel with Alzheimer's disease and dementia progression

The non-digestible polysaccharide acemannan in *Aloe vera* gel is highly butyrate fermentable dietary fiber. The relationship between Alzheimer's disease and dementia with butyrogenic microbiota and butyrate fermented was discussed in a previous report [3]. 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, the hypotensive, antianginal, hypoglycemic and cognition enhancer drugs in a frail female obese patient who was needed in nursing care level 2 on July 2021, moderated into the nursing care level 1 through the daily ingestion of *Aloe vera* juice (AVJ) with above mentioned drugs and multivitamin on April, 2022. Possible association of AVJ with the drugs and multivitamin modulating from the nursing care level 2 into 1 and providing an important role in the modulation of brain homeostasis was achieved.

The anti-inflammatory effects of *Aloe vera* polysaccharide and fermented extracts on human glioblastoma/astrocytoma U373 MG cells

The anti-inflammatory effects of *Aloe vera* (AV) polysaccharide and extracts from the digestion and colonic fermentation of AV were evaluated using an immortal astrocyte cell line (U373MG) that develops a neuro-inflammatory profiles by Tornero-Martinez., *et al* [14]. Cell viability and inflammatory markers were assessed after stimulation with neuropeptide substance P (SP) that activates the pro-inflammatory mitogen-activated protein kinase (MAPK) pathway. Cell viability after SP treatment was over 50% at 10 mg/ml, AV polysaccharide extract from AV, extracts from the digestion: non-digestible fraction of AV non-digestible fraction of polysaccharide extract from AV and extracts from the colonic fermentation of AV, at 4 and 24h. Samples with extracts from the colonic fermentation of AV, at 4 or 24 h showed the highest inhibitory effect on IL-6 production.

Sodium butyrate reduces brain amyloid-levels and improves cognitive memory performance in an Alzheimer' disease (AD) transgenic mouse model at an early disease stage

Fernando., *et al*. [15] investigated the ability of the histone deacetylase inhibitor sodium butyrate (NB) to attenuate memory deficits in the 5xFAD mouse model of AD following a 12-week feeding regimen. 5xFAD mice demonstrate a unique time course of amyloid ß (Aß) pathology, developing Aß plaques as early as 2 months. Male mice were assigned to either a control diet or a NB-supplemented diet which was administered at either 5 mg/kg/day, or 15 mg/kg/day for 12 weeks (each group, N = 15). Behavioral testing (contextual and cued fear conditioning) was undertaken, and brain Aß levels measured at the end of the 12-weeks intervention. NB had profound effects on Aß levels and a 25% increase in fear response in both the cued and contextual testing was observed in the NB-treated animals compared to the control group. The findings suggested that NB warrants further investigation as a potential therapeutic agent in the treatment of cognitive deficits associated with the early stage of AD.

Sodium butyrate improves memory function in an Alzheimer's disease mouse when administered at an advanced stage of disease progression

Dysregulation of histone acetylation has been implicated in the onset of age-associated memory impairment and the pathogenesis of neurodegenerative diseases. Govindarajan., *et al*. [16] showed that severe amyloid pathology correlated with a pronounced dysregulation of histone acetylation (HDAC) in the forebrain of APPS1-21 mice. 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 findings advanced the understanding of the potential applicability of HDAC inhibitors for the treatment of AD and suggested that HDAC inhibitor, butyrate, may have beneficial effects even when administrated long after the onset of disease-associated symptoms.

Sodium butyrate ameliorates the cognitive impairment of Alzheimer's disease by regulating the metabolism of astrocytes

Astrocyte is the most numerous and the largest glial cell in the brain. By transporting energetic fuels, such as lactate and ketones to neuro, astrocytes play a pivotal role in maintaining the cerebral energy homeostasis. Sodium butyrate (NB), an inhibitor on histone deacetylases, has been widely studied and proved the therapeutic effects on Alzheimer's disease (AD) cognitive impairment and provided possible research ideas for mechanism exploration. Wang., *et al*. [17] reported that administration of NB could improve the cognitive impairments induced by Aß25-35 in mice. NB could promote the differentiation of astrocytes towards A2-neuron-protective subtype, astrocyte mitochondrial function, and lactate shuttle between astrocytes and neurons. The findings revealed the effect of NB on astrocytes, which may improve the pathological status of AD and provided an experimental basis for NB treatment of AD.

Cultivable butyrate-producing bacteria of elderly Japanese diagnosed with Alzheimer's disease (AD)

The group of butyrate-producing bacteria within the human gut microbiome may be associated with positive effects on memory improvement and dementia associated diseases. Nguyen., *et al*. [18] investigated fecal samples of four elderly Japanese diagnosed with AD were used to isolate butyrate-producing bacteria. Two-hundred twenty-six isolates were randomly picked, their 16S rRNA genes were sequenced, and assigned into sixty OTUs (operational taxonomic units) based on Basic Local Alignment Search Tool results. Four isolates with less than 97% homology to known sequences were considered as unique OTUs of potentially butyrate-producing bacteria. In addition, 12 potential butyrate-producing isolates were selected from the remaining 56 OTUs based on scan-searching against the PubMed and the Science Direct databases. Those belonged to the phylum *Bacteroidetes* and to the *Clostridial clusters* I, IV, XI, XV, XIV-a within the phylum *Firmicutes*. Fifteen out of the 16 isolates were able to produce butyrate in culture as determined by high-performance liquid chromatography with UV detection. The biochemical and butyrate-producing pathways analysis of butyrate-producers presented in the study may help to characterize the butyrate-producing bacteria community in the gut of AD patients.

Gut microbiota differences in elderly subjects between rural city-Kyotango and urban city- Kyoto in Japan

Naito Y., *et al*. [19] demonstrated that several compositional changes in the gut microbiota are associated with urbanization. Noticeably, an increase was observed in the *Clostridial clusters* XIV-a, butyrate-producing bacteria, at the rural Kyotango city, a long-lived province with various centenarians, compared to the urban Kyoto city. These alterations in the microbiota may provide new insights to consider the relationship between longevity and gut microbiota.

The relationship between the gut microbial population and dementia in outpatients visiting memory clinic

Saji., *et al*. [20] investigated the fecal samples of patients demented and non-demented assessed by terminal restriction fragment length polymorphism (T-RFLP) analysis. The T-RFLP analysis revealed differences in the composition of the gut microbiome: the number

of the percentages of *Bacteroides* was significantly lower in the dementia than non-dementia group. Multivariable analyses showed that the populations of enterotype I and enterotype III bacteria were strongly associated with dementia, independent of the traditional dementia biomarkers.

Three new modifiable risk factors for dementia adding nine factors in dementia prevention

New evidence supported adding three modifiable risk factors- excessive alcohol consumption, head injury, and air pollution- to 2017 Lancet Communication; Livingston G., *et al*. [21] on dementia prevention, intervention, and care life-course model of nine factors (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes and infrequent social contact).

Livingston G., *et al*. [22] stressed that modifying 12 risk factors might possibly prevent or delay up to 40% of dementia even in elderly subjects over 66-years, still remaining 60% unknown risks. Risk reduction may provide the positive participation with butyrate-producing microbiota in elderly dementia subjects. The author emphasized that acting now on dementia prevention, intervention, and care will vastly improve living and dying for individuals with dementia and their families and thus society.

Case Reports

In a previous case report [3], the hypotensive, antianginal, hypoglycemic and cognition enhancer drugs in 73-years old frail female obese patients who was needed in nursing care level 2 on July, 2021, moderated into the nursing care level 1 through the daily ingestion of AVJ with the drugs and multivitamin on April, 2022. In a previous case report [23], a~70 years old male who retired from work upon reaching retirement age, had strong tension around his neck and was diagnosed with PD syndrome in October, 2016. He was administrated Kampo drug; Yokukansan and ingested AVJ and arginine supplement. In February, 2017 he continued to take only AVJ and arginine supplements without the drug administration. Finally, he is well-being QOL in May, 2021. In a previous case report [24], ω-3 polyunsaturated fatty acids, L-Arginine, AVJ supplement and PD-drug to PD patients with/without diabetes showed that PD patients at the stage 3 possible remission in movements changing into the stage 2.

Case report 1: A ~80 years-old female who was diagnosed as Parkinson's disease (PD), had slow movement, making simple tasks difficult and time-consuming of speech, reading and writing, no conversation between the family, and no self-reliance excretion in 2017. She was administered the drug and started to drink *Aloe vera* juice (AVJ, 50 ml/d) and *Aloe vera* supplements for 6 months. Surprisingly, she reads news-paper without any suggestion and her relatives have supported to drink AVJ (50 ml/d) every day and *Aloe vera* supplements since then. Although PD can't be cured perfectly, medications significantly improved her dementia. She is well-being QOL in May, 2023.

Summary and Discussion

Butyrate was shown as one of the main players in the interplay between diet, microbiota, and health conditioning, such as Alzheimer's disease and Alzheimer's dementia progression. In the previous paper we discussed the beneficial effects of butyrate to depressive-like behavior, anemia, fatigue [25] and type-2 diabetes patients and obesity subjects in the case reports [26]. As shown in Lancet Communication in 2020, a possible beneficial efficacy of butyric acid cycle with *Aloe vera* and *A. arborescens* juice ingestion in long time could well serve for the depressive-like behavior, diabetes, obesity, and obesity-prone individuals. Gut microbiota differences in elderly subjects associated with urbanization, notably an increase in *Clostridial clusters* XIV a, butyrate-producing bacteria, at a long-lived providence with various centenarians in Kyotango city [19] provided a new insight to take into consideration of the relationship between longevity and butyrate-producing gut microbiota.

Butyric acid cycle with *Aloe vera* and *A. arborescens* about human immune-modulation could possibly support prevention of Alzheimer's and Parkinson's disease dementia.

In case report 1, a ~80-years-old female who was diagnosed as Parkinson's disease (PD), was significantly improved with the drug administrated, and ingestion of *Aloe vera* juice (AVJ) and aloe-supplement from 2017 to 2023. Her PD dementia was significantly recovered with the drug, AVJ and aloe supplement ingestion. She is a well-being QOL, although she could not cure PD perfectly in May, 2023. Long ingestion of AVJ could mitigate PD's dementia, muscle stretching in the early stage of PD, although PD symptoms can't be cured perfectly. A possible finding of PD in the early stage is necessary to cure PD-dementia.

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Bibliography

1. Dineley KT., *et al*. "Insulin resistance in Alzheimer's disease". *Neurobiology of Disease* 72 (2014): 92-103.
2. Lee JH., *et al*. "Targeting insulin for Alzheimer's disease: Mechanisms, status and potential directions". *Journal of Alzheimer's Disease* 64.1 (2018): S427-S453.
3. Yagi A., *et al*. "Association of butyrate fermented in Aloe vera gel with Alzheimer's disease and Dementia progression. Case report 1: Mitigation of nursing care level". *Journal of Orthopaedic Research* 11.3 (2022): 3713-3718.
4. Lv L., *et al*. "BACE1 (ß-secretase) inhibitory chromone glycosides from Aloe vera and Aloe nobilis". *Planta Medica* 74.5 (2008): 540-545.
5. Gao B., *et al*. "Active constituents from Aloe arborescens as BACE inhibitors". *Yao Xue Xue Bao* 41.10 (2006): 1000-1003.
6. Clementi ME., *et al*. "Aloe arborescens extract protects IMR-32 cells against Alzheimer Amyloid ß-peptide via inhibition of radical peroxide production". *Natural Product Communications* 10.11 (2015): 1993-1995.
7. Kabbash A., *et al*. "Decrease in barbaloin and product of butyric acid fermented by endophytic bacteria in Aloe arborescens leaves". *Journal of Orthopaedic Research* 8.2 (2019): 2853-2857.
8. Hampel H and Shen Y. "Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) as a biological candidate marker of Alzheimer's disease Scand". *Journal of Clinical and Laboratory Investigation* 6.1 (2009). 8-12.
9. Wang Y., *et al*. "Protective effects of Aloe vera extract on mitochondria of neuronal cells and rat brain". *Zhongguo Zhong Yao Zhi* 35.3 (2010): 364-368.
10. Lu J., *et al*. "Effect of aloe polysaccharides pretreatment on the cerebral inflammatory response and lipid peroxidation in severe hemorrhagic shock rats first entering high altitude". *Zhonghua Wai Ke Za Zhi* 50.7 (2012): 655-658.
11. Lewis JE., *et al*. "Efficacy of an aloe-polymannose multi-nutrient complex on cognitive and immune functioning in Alzheimer's disease". *Journal of Alzheimer's Disease* 33 (2013): 393-406.
12. Martin A., *et al*. The Journal of Clinical and Translational Research 3.3 (2017): 337-343.

13. Stillman J., *et al*. "Relationship between brain-derived neurotrophic factor and immune function during dietary supplement of elderly with Alzheimer's dementia". *The Journal of Clinical and Translational Research* 5.2 (2020): 68-75.

14. Tornero-Martinez A., *et al*. "Aloe vera and fermented extracts exhibit an anti-inflammatory effect on human glioblastoma/Astrocytoma U373 MG cells Plant Foods". *Human Nutrition* 77.1 (2022): 37-43.

15. Fernando WMADB., *et al*. "Sodium butyrate reduces brain Amyloid-ß levels and improves cognitive memory performance in an Alzheimer's disease transgenic mouse model at an early disease stage". *Alzheimer's Disease* 74.1 (2020): 91-99.

16. Govindarajan N., *et al*. "Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression". *Journal of Alzheimer's Disease* 26.1 (2011): 187-197.

17. Wang C., *et al*. "Sodium butyrate ameliorates the cognitive impairment of Alzheimer' disease by regulating the metabolism of astrocytes". *Psychopharmacology* 239.19 (2022): 215-227.

18. Nguyen TTT., *et al*. "Cultivable butyrate-producing bacteria of elderly Japanese diagnosed with Alzheimer's disease". *Indian Journal of Microbiology* 56.10 (2018): 760-771.

19. Naito Y., *et al*. "Gut microbiota differences in elderly subjects between rural city-Kyotango and urban city Kyoto: an age-gender-matched study". *Journal of Clinical Biochemistry and Nutrition* 65.2 (2019): 125-131.

20. Saji N., *et al*. "Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in". *Japan Scientific Reports* 9 (2019): 1008.

21. Livingston G., *et al*. "Dementia prevention, intervention, and care 2017. Report of the lancet communication". *Lancet* 390.10113 (2017): 2673-2734.

22. Livingston G., *et al*. "Dementia prevention and care 2020. Report of the lancet communication". *Lancet* 396.10248 (2020): 413-416.

23. Yagi A., *et al*. "Epigenetic roles of short chain fatty acids as beneficial modulators in the neuroendocrine systems Case reports: Influence of Aloe vera juice to brain homeostasis". *Journal of Gastroenterology and Hepatology Research* 10.5 (2021): 3571-3576.

24. Yagi A., *et al*. "Nutraceutical Aloe vera gel scaffolds for supporting a healthy muscle movement". *Journal of Gastroenterology and Hepatology Research* 7.6 (2018): 2720-2728.

25. Yagi A., *et al*. "Putative role of butyrate fermented in Aloe vera gel for depressive-like behavior; Case report: Remission of depressive-like behavior, anemia, fatigue and cystitis". *Journal of Gastroenterology and Hepatology Research* 11.4 (2022): 3748-3752.

26. Yagi A., *et al*. "Prophylactic role of butyrate in Aloe vera gel to type-2 diabetic patients and obesity subjects: Case reports of obesity-prone individuals". *EC Clinical and Medical Case Reports* 6.1 (2023): 72-77.

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