

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2021.10.1021

Journal of GHR 2021 October 21; **10(5)**: 3571-3576
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

REVIEW

Epigenetic Roles of Short Chain Fatty Acids as Beneficial Modulators in the Neuroendocrine Systems Case Reports: Influence of Aloe vera Juice to Brain Homeostasis

Akira Yagi¹, PhD; Megumi Hasegawa²; Miiko Mikami³; Suzuka Ataka⁴, MD, PhD

1 Special adviser 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. Former a nurse, Sapporo, Hokkaido, Japan;

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

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

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

Received: June 20, 2021

Revised: July 15, 2021

Accepted: July 17, 2021

Published online: October 21, 2021

ABSTRACT

Recent discoveries have focused on the linking of gut-microbiome and the brain, which are achieved through several pathways, such as vagus nerve, immune system and endocrine system (hypothalamic-pituitary-adrenal axes). In present review we discussed the microbial metabolites, short chain fatty acids, in gastrointestinal functional, neuro-immune regulation and their role in stress-induced behavioral and physiological alterations. Furthermore we discussed the impact

on the corticoid action of micRNAs. In case reports we showed that Kampo medicine, Yokukansan with aloe vera juice (AVJ) as an adjuvant exhibited possible efficacy for modulation in brain homeostasis and the drug privation with AVJ provided health maintenance in patient with Hashimoto's clinical history and well-being QOL.

Key words: *Aloe vera*; Short chain fatty acids; Butyric acid; Psychologic health modulator; Hypothalamic-pituitary-adrenal axis; micRNAs; Case reports

© 2021 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Yagi A, Hasegawa M, Mikami M, Ataka S. 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* 2021; **10(5)**: 3571-3576 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3192>

INTRODUCTION

Short chain fatty acids (SCFAs) are primarily derived from fermentation of dietary fibers and in case of *Aloe vera* leaf the endophytic bacteria produced SCFAs, butyric acid. SCFAs play a pivotal role in host gut, metabolic and immune function and all these factors have been demonstrated to be adversely affected by stress. The effect of aloe vera in animal models of learning and memory, depression, and locomotion was investigated by Halder et al^[1], and the authors reported aloe vera ingestion enhances learning and memory, and alleviates depression in mice. Van de Wouw et al^[2] showed that acute stress-induced hyperthermia and corticosterone levels in chronically stressed mice are ameliorated by SCFA supplementation. The results present novel insights into mechanisms underpinning the influence of gut microbiota on brain homeostasis, behavior and host metabolism, informing the development of microbiota-targeted therapies for stress-related disorders. The pathways of gut-brain bidirectional communication

with the emphasis on the immune system, the vagus nerve, and the endocrine system were discussed by Reyes *et al*^[3]. This communication involve the immune system, which not only supports the tolerance towards the microbiome ecosystems residing in the gastrointestinal tract but also can react to dysbiosis and leaky gut, thus relaying this information to the central nerve system. The sedative and hypnotic effects of the aqueous extract of *Aloe vera* were investigated by Abdollahnejad *et al*^[4]. The authors showed that aloe extract has sedative-hypnotic effects on both functional and electrical (the electroencephalography analysis) activities of the brain, revealing the efficacious effects of aloe vera extract on the brain activities.

In previous paper focusing on aloe components, such as aloemodin, aloin, short chain fatty acids, butyrate fermented, and miRNAs to prevent Alzheimer's disease (AD) and Parkinson's disease (PD), we described that aloe components modulate senescence-related pathological condition^[5,6]. 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 SCFAs; butyric acid. The alteration of 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. In previous paper 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^[7].

A possible link between the gut microbiota and autism spectrum disorders (ASD) was reviewed by Srikantha and Mohajeri^[8]. The authors presented several epidemiologic and *in vivo* studies for the involvement of different microbes in the ASD pathology. Mohajeri *et al*^[9] reviewed on relation between the gut microbiome and brain function. Butyrate is the most important SCFA in humans as it exhibits neuroprotective features. It promotes memory formation and neuronal plasticity through epigenetic modulation, suggesting that an involvement of increased acetate and propionate and decreased butyrate in the pathophysiology of ASD. In our previous review the efficacy of aloe fermented butyrate to ASD was reported^[10].

Hypothalamic-pituitary-adrenal (HPA) axis activation is one of the key responses following physiological stress. Corticosteroid provides negative feedback to the HPA system at the level of the hippocampus, hypothalamus, and pituitary gland by activating glucocorticoid (GC) receptors. The dysfunction of the HPA axis is one of the most widely accepted hypothesis of anxiety, which is a central system in maintaining neuroendocrine equilibrium. The HPA axis has an established association with anxiety, including physiological homeostasis and the stress response. Disturbances in this system result in severe hormonal imbalances, which may be strongly implicated in the pathology of major depressive disorder.

Micro RNAs (miR) are small, non-coding RNAs that typically bind to specific sequences in the 3'-untranslated regions (3'-UTRs) of targeted miRs to negatively fine-tune protein expression. miRs have recently emerged as a key regulators of metabolism and many considered to be biomarkers of depression or anxiety. miRs play an important role in mediating anxiety via GC hormone signaling^[11].

Present review described the role of butyrate fermented in *Aloe vera* for HPA axis and miRs in anxiety and stress. Case reports exhibited that Kampo medicine with *Aloe vera* juice-adjuvant as beneficial modulators and the drug privation with AVJ plays a big role to maintain the brain homeostasis.

BENEFIT OF SHORT CHAIN FATTY ACIDS AS MODULATORS OF PSYCHIATRIC HEALTH

A link between enteric microbiota and brain function

Ingestion of probiotics modulates the processing of information that is strongly linked to anxiety and depression, and influences the neuroendocrine stress response. Schmidt *et al*^[12] resulted that the salivary cortisol awakening response was significantly lower after Bimuno-galacto-oligosaccharides (B-GOS) intake compared with placebo in 45 healthy volunteers. The authors explored the effects of two probiotics (fructo-oligosaccharides and B-GOS) on the secretion of the stress hormone, cortisol and emotional processing in healthy volunteers. Participants showed decreased attentional vigilance to negative versus positive information in a dot-probe task after B-GOS compared to placebo intake.

Gut microbiota is currently viewed as a key regulator of a fluent bidirectional dialogue between the gut and the brain (gut-brain axis, GBA). A number of preclinical studies have suggested that the microbiota and its microbiome may play a key role in neurodevelopmental and neurodegenerative disorders. GBA involves endocrine and neural pathways and interaction with gastrointestinal tract (GI) immune system and the gut microbiota. The GBA plays a crucial role in the modulation of the physiological functioning of the GI tract and the brain. This complex communication system is extremely sensitive to stress. Cenit *et al*^[13] discussed a role of the gut microbiota in neuropsychiatric disorders and the state of the art regarding the mechanisms underlying its contribution to mental illness and health.

Probiotics and prebiotics: short chain fatty acids, as mostly beneficial modulators of the neuroendocrine system: A cross-talk between the hypothalamic-pituitary-adrenal axis and the gut-brain axis

Stress has different effects on the body and endocrine system. The recovery of adrenal function and improvement of chronic fatigue syndrome (CFS) systems through a connection between the hypothalamic-pituitary-adrenal (HPA) activity and CFS is the most important factor. One of the systems that are emerging to closely interact with the gut microbiota is the body's major neuroendocrine system that control various body processes in HPA axis. The effects of acute and chronic of immobilization stress and aloe vera gel water-extract on serum levels of thyroid stimulating hormone (TSH), thyroxin (T4) and triiodothyronine (T3) in male rats were investigated by Ahmadi *et al*^[14]. Acute immobilization enhanced levels of T3, T4 and TSH and the use of aloe vera extract prevented this kind of increase. The effects of immobilization stress along with aloe vera gel extract on controlling or strengthening the effects of immobilization stress on thyroid gland function were evaluated. In previous paper^[15] the investigation of chronic fatigue syndrome with aloe vera juice with L-arginine, in long-term ingestion influenced by the intestinal microbiota were discussed and the benefits showed big promises to CFS in adult subjects.

Farzi *et al*^[16] reviewed the interaction is of pivotal importance; as various disorders of the microbiota-gut-brain axis are associated with dysregulation of the HPA axis. Furthermore the authors discussed microbial short chain fatty acids (SCFAs) are emerging to be of special importance in a variety of physiological and pathophysiological processes.

Dalile *et al*^[17] investigated the role of SCFAs in modulating psychobiological processes that underlie the development of

stress- and anxiety-related disorders in human. In the triple-blind, randomized, placebo-controlled intervention trial, the authors examined in a parallel group design the effects of one-week colonic SCFAs mixture delivery in dose equivalent to fermentation of 10g or 20g of arabinoxylan oligosaccharides on responses to psychological stress and fear tasks in 66 healthy men. The authors demonstrated that low and high doses of SCFAs significantly attenuated the cortisol response to psychological stress compared to placebo. Both doses of SCFAs increased serum SCFA levels and this increase in circulating SCFAs co-varies significantly with the attenuation of the cortisol response to psychological stress.

The gut microbiota can activate the HPA axis through several mediators that cross the blood-brain barrier and include microbial antigens, cytokines and prostaglandins. Mislak *et al*^[18] described that the evidence that various microbial species can affect ileal corticosterone production that may impact the activity of the HPA axis. Some metabolites released by various microbes, e.g., SCFAs, can attenuate the HPA response, and the HPA axis activation can impact the gut microbiota and intestinal permeability. The authors discussed various mechanisms linking the gut microbiota with the HPA axis activity and summarized current evidence for a cross-talk between the gut-brain axis and the HPA axis from studies of patients with mood and psychotic disorders.

Gut symptoms are common in individuals with depressive disorders and recent data indicated relationship between gut microbiota and psychiatric health. Muller *et al*^[19] investigated potential associations between SCFAs and self-reported depressive and gut symptoms in young adults. Fecal samples from 164 individuals, of which 125 were patients with psychiatric disorders, were analyzed for SCFAs. Then the authors compared SCFA ratios to dimensional measures of self-reported depressive and gut symptoms. Gut symptoms are common in individuals with depressive disorders, and the authors showed that shifts in SCFAs may have relevance for both depressive symptoms and gut symptoms in young adults. The results indicated relationships between gut microbiota and psychiatric health.

Prevention of psychological stress-induced memory dysfunction in mice by *Lactobacillus johnsonii* BS15

The issue of whether psychological stress induced memory dysfunction can be prevented via *Lactobacillus johnsonii* BS15 pretreatment to modulate the gut-brain-axis was investigated by Wang^[20]. The results indicated that *L. johnsonii* BS15 exerted beneficial effects on the hippocampus by modulating memory-related functional proteins, especially those related to synaptic plasticity, such as brain-derived neurotrophic factor and stem cell factor. The modulation of the gut-brain axis by *L. johnsonii* BS15 could be considered a promising non-invasive treatment modality for psychological stress-induced memory dysfunction.

THE ROLE OF ACTIVE COMPONENTS FROM ALOE VERA; SCFAS FERMENTED, AND MICRNAS ON THE BASIS OF GUT-MICROBIOTA-BRAIN AXIS

Previous articles focused on aloe components, SCFAs, and micRNAs presented the modulation of Alzheimer's disease and Parkinson's disease in age-related senescent inflammation^[21,22]. Hypothalamus-pituitary-adrenal (HPA) axis activation is one of the key responses following physiological stress. Corticosteroids provide negative

feedback to the HPA system at the level of the hippocampus, hypothalamus, and pituitary gland by activating glucocorticoid receptors (GRs).

Recent studies revealed that micRNAs (miRs) are epigenetic regulators of gene expression and non-coding RNAs that inhibit the translation and/or decrease the stability of their target miR, and indicated that miR are involved in various functions such as embryonic development, differentiation, and neural plasticity. Shimizu *et al*^[23] evaluated that Kampo medicine Yokukansan (YKS) administered to the patients who show symptoms such as nervousness, short-tempered behavior, irritability, can affect psychological symptoms such as depression and anxiety that are associated with stress responses. In this study the authors evaluated the effect of YKS on miR-18 and -124a and GR levels in mice exposed to stress and YKS pretreatment normalized elevated plasma corticosterone levels in stress-exposed mice. YKS normalizes GR protein levels by regulating miR-18 expression in the hypothalamus, thus normalizing HPA axis activity following stress exposure.

Prolonged exposure to bullying behaviors may give to symptoms such as anxiety, depression and chronic pain. A consistent body of evidence shows that bullying is associated with a subsequent increase in health complaints, including self-reported pain. Using rat models of social stress, Jacobsen *et al*^[24] identified miR-146a, miR-30c and miR223 as potentially important gene regulatory molecules that may be involved in the stress response. Human genotypes affecting the expression of mature miR-30c and miR-223 had a moderating effect on the association between exposure to bullying and pain. Subjects with the miR-30c rs928508 GG genotype had a significant stronger association between exposure to bullying behaviors and pain than other subjects.

Regulation of behavioral response to stress by miR-690

Stress is a state in which homeostasis cannot be maintained, and both physical and psychological stressors have been reported to cause alteration in the endocrine system. Psychiatric disorders are affected by genetic susceptibility and environmental adversities. The regulation of gene expression under certain environments, such as stress, is a key issue in psychiatric disorders. MiRNAs have been implicated as post-transcriptional regulators of several biological processes, which can be differentially controlled through the targeting of multiple miRNAs. Park *et al*^[25] identified a significant increase in the expression of miRNA-690 (miR-690) in the medial prefrontal cortex of FK506-binding protein 51 knock-out mice. The authors showed that miR-690 might play a role in stress resilience and could provide new insights into the epigenetic regulation of stress-associated biological functions and diseases, such as depression and post-traumatic stress disorder.

The Hypothalamic-pituitary-adrenal (HPA) axis in neuroendocrine responses to stress

Stress can significantly impact the microbiota-gut-brain axis at all stage of life. In response to stress, corticotropin-releasing factor plays a central role in the stress response by regulating the HPA axis. Smith *et al*^[26] discussed the role of the HPA axis in the integration of adaptive responses to stress, and identified the major neuronal and endocrine systems that contribute to the regulation of the HPA axis and the maintenance of homeostasis in the face of aversive stimuli. Colon-derived SCFAs modulate HPA response of psychosocial stress; cortisol awakening response in 66 healthy human subjects^[17].

EFFECT OF ALOE VERA GEL EXTRACT ON DEPRESSION IN PREDIABETES PATIENTS AND MICE MODEL

Depression is one of the major mood disorders that lead to development of type 2 diabetes in pre-diabetic patients. Prediabetes state is a condition of abnormal blood glucose level between normal and diabetic states that involves impaired fasting glucose and impaired glucose tolerance. Foadoddini *et al.*^[27] examined the effect of aloe vera gel extract on depression in prediabetes 72 patients by a double blind randomized controlled trial study. The mean depression scores in the 500mg treated aloe vera extract powder decreased significantly in Beck Depression inventory before and eight weeks after the intervention. The Iranian Registry of Clinical Trial: IRCT 2013041112984N1.

The antidepressant effects of aloe vera hydro-alcohol extract at different concentrations were compared with the fluoxetine (the selective serotonin reuptake inhibitor)-treated and the control groups of mice using forced-swimming test; FST and open box test; OBT test by Salehi *et al.*^[28]. Aloe vera extract has favorable antidepressant effects on mice as compared to the fluoxetine-treated and the control groups on FST.

CASE REPORTS: INFLUENCE OF ALOE VERA JUICE TO BRAIN HOMEOSTASIS

Case 1

A ~sixty-year female who had deep headache, strong tension on her neck and upper back, tinnitus and palpitation, showed over 180 mm/Hg on systolic blood pressure during ten years. She took a hypotensive drug; telmisartan, but the blood pressure continued to show over 180 mm/Hg on systolic blood pressure. She stopped to take telmisartan and took Kampo medicine; Yokukansan (YKS) and aloe vera juice (AVJ; 300 ml/day) on September, 2020. On November, 2020, the systolic and diastole blood pressure showed 154/100 mm/Hg. She took Kampo medicine YKS and AVJ when she only feels stress. On April, 2021 the systolic and diastole blood pressure showed 140/90 mmHg, when she took only AVJ (330 ml/day). Then she recovered from illness and had well-being QOL.

Case 2

A ~sixty-year female who is suffering from insomnia during 15-years because of her stress work, took a tranquilizer DEPAS (etizolam, 1mg/day). However, her symptom; headache, tension on her neck and upper back, fatigue and sleep deprivation with ~35°C body temperature, continued for several months to May 2016. On September, 2016, she started to take YKS with AVJ (600 ml/day) and etizolam (0.25 mg/three times a day). Then she had 5 hours sleeping time a day and felt a decreased level of tension on her neck and fatigue. She became active but she had recurrence of ill on May, 2020, because she had an unhappy of her relative death. She had a continuation of insomnia and strong stress, and started to take AVJ and YKS on July, 2020. She recovered from her insomnia and had a well-being QOL to June, 2021.

Case 3

A ~70 year male who retired from work upon reaching retirement age, had strong tension around his back and was diagnosed Parkinson's disease (PD) syndrome. It comes from the pain of spinal stenosis. He had spinal canal stenosis in his health history. To prevent

the tension he had taken analgesic drug for 5-6 years, but still had mental stress. On October, 2016 he diagnosed as PD syndrome. Then he took YKS and AVJ supplements with arginine (10 g/day). Since then he recovered from freezing of gait and muscle rigidity, and the pain due to spinal canal stenosis. On February, 2017, he continued to take only AVJ and arginine supplement and impaired postural reflexes. Finally he is well-being QOL without drug administration and PD syndrome on May 2021.

Case 4

A 44 year male diagnosed to Hashimoto's disease since 36 year-old, had stress indicator 69.3. During for several months, stress indicator showed 72.3 from his life-troubles. He had bad tremor due to continuous insomnia and severe tremor, and was diagnosed to panic syndrome. He administrated DEPAS 0.5 (etizolam), Loxonin (loxoprofen sodium hydrate), Thyradin S50 (levothyroxine sodium), Lorcam (lornoxicam), Tredomin D25 and aloe vera juice (AVJ) 100ml/day for seven years. On 51 year-old he only took thyradin S50 due to normal level of blood examination, and AVJ 150ml/day. On 58 year-old he only took AVJ 150ml/day and had well-being QOL to June, 2021.

DISCUSSION ON CASE REPORTS 1-4

Two female patients in case report 1 and 2 were just around the onset of the postmenopausal syndrome and were in high levels of the stress sensitivity. The medicine did not exhibit complete effect because of their high mental stress. To mitigate the mental stress administration of YKS with AVJ adjuvant revealed the moderate effect for two depressed females. The anti-stress effect of YKS was discussed about molecular mechanisms regulating glucocorticoid receptors in the hypothalamus^[23], and the brain homeostasis was demonstrated by use of Kampo medicine YKS. In case report 3 male patient had a strong stress due to spinal stenosis after his retirement. YKS with AVJ and arginine supplement was administered to eliminate pain due to spinal stenosis. Parkinson's disease (PD) syndrome in male patient has disappeared without PD-medicine administration. In case report 4, male patient with Hashimoto's disease history was prescribed several medicines. Finally he decided to drug deprivation, and only ingested daily AVJ. He had well-being QOL in 58-years old.

In our previous paper^[29] we described that the ingestion of AVJ for seven years in 61-years old frail female increased 3.4 and 2.4 fold higher in the comparative fecal content of butyrogenic prebiotic *Faecalibacterium spp.* and *Clostridium spp.*, respectively, exhibiting the potent immune regulation function in the colon of healthy human. Daily ingestion of AVJ for long time may support the beneficial gut-microbiome correlation in health maintenance. The patient with Hashimoto's disease in his clinical history in case report 4, alleviated depression and had well-being QOL by use of daily AVJ ingestion.

SUMMARY

We reported that daily intake of the butyric acid fermentation extract from Aloe vera inner gel with endophytic bacteria may provide the possible potential preventive and therapeutic approaches for human health^[30,31].

In present report we discussed at first, short chain fatty acids (SCFAs) and hypothalamic-pituitary-adrenal axis (HPA), and secondary, micRNA, HPA axis and stress for homeostasis. The research that linked gut and brain and emotion referred to the Gut-Brain-Axis. Gut bacteria and the produced SCFAs; butyric acid, have been shown to impact our mood and response to stress by affecting

the Gut-Brain-Axis, the hypothalamic-pituitary-adrenal axis (the body's stress responses system) and the levels of inflammation in the body. In case reports 1-3, Kampo medicine; Yokukansan with aloe vera juice-adjunct exhibited a possible efficacy to brain homeostasis. Homeostasis is impacted in many ways by drug usage and withdrawal. In case report 4, it was suggested that drug deprivation may be partially supported with AVJ supplementation by producing butyric acid. We revealed that AVJ supplementation may support Kampo medicine and provide an important play in the modulation of brain homeostasis and the drug privation.

ACKNOWLEDGEMENT

The authors express our deep appreciation for Mr. A. Mukaitani, Chairperson of Japan Aloe Science Association, to support to set-up case reports.

REFERENCES

- Halder S, Mehta AK, Mediratta PK. *Aloe vera* improves memory and reduces depression in mice. *Nutritional Neuroscience* 2013; **16**: 250-254 [PMID: 23394255]
- Van Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, Clarke G, Stanton C, Dinan TG, Cryan JF. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations *The J. of Physiology* 2018; **596(20)**: 4923-4944 [PMID: 30066368] [DOI: 10.1111/JP276431]
- Reyes REN, Zhang Z, Gao L, Asatryan L. Microbiome meets microglia in neuroinflammation and neurological disorders *Neuroimmunol Neuroinflammation* 2020; **7**: 215-233 [DOI: 10.20517/2347-8659.2020.13]
- Abdollahnejad E, Mosaddegh M, Nasoohi S, Mirnajafi-Zadeh J, Kamalinejad M, Faizi M. Study of sedative-hypnotic effects of *Aloe vera* L. aqueous extract through behavioral evaluations and EEG recording in rats *Iran J. Pharm Res.* 2016; **15(1)**: 293-300 [PMID: 27610170]
- A Yagi, M Hasegawa, S Ataka Prophylactic role of Aloe components, butyrate fermented, micrnas, and hyaluronan on Alzheimer's disease and Parkinson's disease, and osteoarthritis in knee joints: case reports of Aloe vera juice ingestion producing intestinal butyrogenic microbiome and bone regeneration *J. of GHR* 2021; **10(1)**: 3398-3406 [DOI: 10.17554/j.issn.2224-3992.2020.10.983]
- A Yagi, S Ataka, BP Yu Putative roles of aloe ingredients in aging and age-related diseases: Management of microbial senoinflammatory process *J. of GHR* 2021; **10(2)**: 3460-3465 [DOI: 10.17554/j.issn.2224-3992.2021.10.1003]
- A Yagi and BP Yu Fermented butyrate of *Aloe vera* and *A. arborescens* by endophytic bacteria: Its prophylactic action on brain insulin resistance *J. of GHR* 2019; **8(4)**: 2896-2901 [DOI: 10.17554/j.issn.2224-3992.2019.08.836]
- Srikanta P and Mohajeri MH. The possible role of the microbiota-gut brain-axis in autism spectrum disorder *Int. J. of Molecular Sci.* 2019; **20(9)**: 2115
- Mohajeri MH, Relationship between the gut microbiome and brain function *Nutrition Reviews.* 2018; **76**: 481-496
- M Hasegawa, A Yagi, S Ataka Efficacy of aloe fermented butyrate to autism spectrum disorders *EC Clinical and Medical Case Reports* 2020;**3(3)**: 01-09
- Clayton SA, Jones SW, Kurowska-Stolarska M, Clark AR. The role of microRNAs in glucocorticoid action *J. Biol. Chem.* 2018; **293(6)**: 1865-1874. [DOI: 10.1074/jbcR117.000366]
- Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ. Prebiotic intake reduces the walking cortisol response and alters emotional bias in the healthy volunteers *Psychopharmacology* 2013; **232**: 1793-1801 [DOI: 10.1007/s00213-014-3810-0]
- Centit MC, Sanz Y, Codoner-Franch P. Influence of gut microbiota on neuropsychiatric disorders *World J. Gastroenterol.* 2017; **23(30)**:5486-5498 [PMID: 28852308]; [DOI: 10.3748/wig.v23.i30.5486]
- Ahmadi R, Abbasi Z, Asgary V. The effects of acute and chronic immobilization stress and aloe vera extract on serum levels of TSH, T3 and T4 in male rats *Zah J. Res Med Sci.* 2015; **17(3)**: e1133 [DOI: 10.5812/zjrms.1133]
- A Yagi, S Ataka Putative prophylaxes of aloe vera juice with L-arginine to chronic fatigue syndrome *J. of GHR* 2016; **5(2)**: 1950-1956 [DOI: 10.17554/j.issn.2224-3992.2016.5.603]
- Farzi A, Frohlich EE, Holzer P. Gut microbiota and the neuroendocrine system *Neurotherapeutics.* 2018; **15(1)**: 5-22 [PMID: 29380303]; [DOI: 10.1007/s13311-017-0600-5]
- Dalile B, Vervliet B, Bergonzelli G, Verbeke K, Van Oudenhove L. Colon-delivered short-chain fatty acids attenuate the cortisol response to psychological stress in healthy men: a randomized, placebo-controlled trial *Neuropsychopharmacology* 2020; **45**: 2257-2266
- Misiak B, Loniewski I, Mojciech W, Frydecka D, Szulc A, Rudzki L, Samochovec J. The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Neuropharmacology and Biological Psychiatry* 2020; **102**: 109951 [DOI: 10.1016/j.pnpbp.2020.109951]
- Muller B, Rasmuson AJ, Just D, Jayarathna S, Moazzami A, Novicic ZK, Cunningham JL. Fecal short chain fatty acid ratios are related to both depressive and gastrointestinal symptoms in young adults *medRxiv* 2020 April 29. [DOI: 10.1101/2020.04.24.20078352]
- Wang H, Sun Y, Xin K, Zhang T, Sun N, Ni X, Zeng D, Bai Y. *Lactobacillus johnsonii* BS15 prevents psychological stress-induced memory dysfunction in mice by modulating the gut-brain axis *Front.Microbiol.* 2020; 13 August [DOI: 10.3389/fmicb.2020.01941]
- A Yagi, M Hasegawa, S Ataka. Prophylactic role of Aloe components, butyrate fermented, Micrnas, and hyaluronan on Alzheimer's disease, Parkinson's disease, and osteoarthritis in knee joints: Case reports of Aloe vera juice ingestion producing intestinal butyrogenic microbiome and bone regeneration *J. of GHR* 2021; **10(1)**: 3398-3406 [DOI: 10.17554/j.issn.2224-3992.2020.10.983]
- A Yagi, S Ataka, BP Yu. Putative roles of Aloe ingredients in aging and age-related diseases: Management of microbiota senoinflammatory process *J. of GHR* 2021; **10(2)**: 3460-3465 [DOI: 10.17554/j.issn.2224-3992.2021.10.1003]
- S Shimizu, T Takahashi, T Takeda, M Tohyama, S Miyata The Kampo medicine Yokukansan decreases micrRA-18 expression and recovers glucocorticoid receptors protein expression in the hypothalamus of stressed mice *BioMed Research Int.* 2015; Article ID 797280 [DOI: 10.1155/2015/797280]
- Jacobson DP, Eriksen MB, Rajalingam D, Nymoen I, Nielsen MB, Einarsen S, Gjerstad J. Exposure to workplace bullying, microRNAs and pain evidence of a moderating effect of miR-30c rs928508 and miR rs3848900 *STRESS* 2020; **23(1)**: 77-86 [DOI: 10.1080/10253890.2019.1642320]
- Park J, Lee J, Choi K, Kang HJ. Regulation of behavioral response to stress by microRNA-690 *Mol Brain* 2021; **14**: 7 [DOI: 10.1186/s13041-021-00728-3]
- Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress *Dialogues Clin Neurosci.* 2006; **8(4)**: 383-395 [PMID: 17290797]; [DOI: 10.31887/DCNS.2006.8.4/ssmith]
- Foadoddini M, Mofrad SA. Effect of Aloe vera extract on depression in people with prediabetes *Mod Care J.* 2020; **17(2)**: e100927 [DOI: 10.5812/modern.100927]
- Salehi B, Biazar E, Jahromi MH, Romani HA. Antidepressant

- effects of aloe vera hydro-alcoholic extract on mice model *J. of Paramedical Science* 2011; 2(3) ISSN 2008.-4978
29. Yagi A, Hasegawa M, Ataka S. Prophylactic role of Aloe components, butyrate fermented, miRNAs, and hyaluronan on Alzheimer's disease, Parkinson's disease, and osteoarthritis in knee joints: Case reports of Aloe vera juice ingestion producing intestinal butyrogenic microbiome and bone regeneration *J. of GHR* 2021; **10(1)**: 3398-3406 [DOI: 10.12554/j.issn.2224-3992.2020.10.983]
 30. Yagi A, Kabbash A, Al-Madboly LA Short chain fatty acids from fermented by endophytic bacteria in Aloe vera leaf rind and gel *J. of GHR* 2016; **5(4)**: 2122-2124 [DOI: 10.17554/j.issn-2224-3992.2016.05.658]
 31. Yagi A, Yu BP. Immune modulation by microbiota sources: Effects of Aloe vera gel and butyrate *J. of GHR* 2018; **7(5)**: 2681-2689 [DOI: 10.17554/j.issn.2224-3992.2018.07.791]