

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2022.11.1043

Journal of GHR 2022 February 21; **11**(1): 3647-3651
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

REVIEW

Prophylactic Role of Butyrate Fermented in Aloe Vera Gel on Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder, Insomnia, and Basedow's Disease: Case Reports of Aloe Vera Juice Ingestion

Akira Yagi¹, PhD; Megumi Hasegawa²; Kosuke Shiba³, MD

1. Editor-in-Chief of Journal of Gastroenterology and Hepatology Research; Professor Emeritus of Fukuyama University, Hiroshima, Japan; Special Adviser of Japan Aloe Science Association;

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

3 A visiting doctor in Yokohama city, Kanagawa-ken, Japan.

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

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

Email: 0131akirayagi@gmail.com

Telephone: +81-92-938-2717

Received: November 26, 2021

Revised: December 18, 2021

Accepted: December 20, 2021

Published online: February 21, 2022

ABSTRACT

The microbiota and the brain communicate with each other via various routes including the immune system and the vagus nerve and the enteric nerve system, involving microbial metabolites such as short chain fatty acids. We focused on understanding the mechanisms underlying the microbiota- gut-brain axis and attempted to elucidate the potential of butyrate for development of the strategies for brain disorders. In case reports 1-3, aloe vera juice (AVJ) successive ingestion modulates a biological defense system via immunity and

AVJ improves the brain disorders associated with immunological abnormalities. In case report 4, successive AVJ ingestion demonstrated the mitigation of side effect and withdrawal of steroid drug in chronic inflammatory demyelinating polyneuropathy patient.

Key words: Prophylactic role; Aloe vera gel; Butyrate fermented; Brain homeostasis; Case reports

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Yagi A, Hasegawa M, Shiba K. Prophylactic Role of Butyrate Fermented in Aloe Vera Gel on Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder, Insomnia, and Basedow's Disease: Case Reports of Aloe Vera Juice Ingestion. *Journal of Gastroenterology and Hepatology Research* 2022; **11**(1): 3647-3651 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3260>

INTRODUCTION

Long-term ingestion of aloe vera gel juice (AVJ) ingestion, containing acemannan: acetylated aloe poly-manno-saccharide (β -mannan), influences the microbial activity in human gut. The prebiotic activity of AVJ was judged by participating of short chain fatty acids, during 24hrs incubation with *Lactobacillus fermentum* in vitro^[1]. The successive ingestion of AVJ provided high concentration of butyrogenic microbiome *Faecalibacterium* spp, and *Clostridium* spp. in fecal^[2]. The corrective understanding of β -mannan saccharification in the human colon is limited to a few keystone species, which presumably liberate low-molecular-weight β -manno-oligosaccharide (MOS) fragment that become directly available to the surrounding microbial community. Lindstad et al^[3] showed that commensal butyrate-producing bacteria belonging to the *Firmicutes* phylum are abundant in the human gut and are crucial for maintaining health. The author found the mechanical understanding of the MOS utilization capability for *F. prausnitzii* that may be exploited to select dietary formulations specifically boosting this beneficial symbiont, and thus butyrate production, in the gut. The results obtained provide a significant advance in the knowledge of β -mannan metabolism and the degree

to which its degradation is mediated by cross-feeding interactions between prominent beneficial microbes in the human gut.

In the earlier report, the fermentation by endophytic bacteria in aloe vera gel provided short chain fatty acids, butyric acid^[4]. And two case reports in the previous paper^[2] suggested that aloe vera gel juice successive ingestion keeps healthy life and well QOL through the intestinal production of prebiotic butyrogenic gut microbiome, *Faecalibacterium* spp., and could play a beneficial role for tissue repair and bone regeneration. The research that linked gut and brain and emotion referred to the gut-brain-axis was described in the previous paper^[5]. Present review is focused on prophylactic role of butyrate by successive ingestion of AVJ to neurological disorders, Basedow's disease and case reports.

AUTISM SPECTRUM DISORDERS ASSOCIATED WITH IMMUNOLOGICAL ABNORMALITY INVOLVING CYTOKINES AND INFLAMMATION

Autism spectrum disorders and allergic disease, and autoimmune comorbidity

An investigation of the association between autism spectrum disorders (ASD) and allergic/ autoimmune diseases achieved in the National Health Insurance Database from 1996 to 2010. The results supported the association between ASDs and allergic diseases, and autoimmune comorbidities (type I diabetes and Crohn's disease). Chen et al^[6] highlighted that patients with ASDs had a higher prevalence and risk of allergic disease than the control, and validated the possible association of ASDs with type I diabetes and Crohn's disease.

Alteration of gut microbiota and short chain fatty acids (SCFAs) in Chinese children with autism spectrum disorder

Liu et al^[7] sequenced the bacterial 16S rRNA gene, detected fecal short chain fatty acids (SCFAs), assessed GI symptoms and analyzed the relationship between the gut microbiome and fecal SCFAs in autistic and neuro-typical individuals. The author resulted that the compositions of the gut microbiota and SCFAs were altered in ASD individuals, and found lower levels of fecal acetic acid and butyric acid and higher level of fecal valeric acid in ASD subjects. It was suggested that the gut microbiota contributes to fecal SCFAs and constipation in autism. Modulating the gut microbiota, especially butyrate-producing bacteria, could be a promising strategy in the search for alternatives for the treatment of ASD.

Disturbances of cytokines profile and alterations in gut microbiota abundance in ASD children and adolescents

Cao et al^[8] enrolled 45 ASD individuals and 41 healthy control (HC) subjects with ages ranging from 2 to 19 years. The author found ASD group subjects have significant higher plasma levels of cytokines comparing to HC. The ASD gut microbiome is characterized by reduced levels of several beneficial microbiota including *Bacteroides* and *Lachnospiraceae*. The author proposed that the association between the disturbances of specific cytokines and alterations in gut microbiota abundance in observed children and adolescents with ASD provides additional evidence on the induction of aberrant pro-inflammatory mechanism in ASD and its early diagnosis. It is documented that butyrate can ameliorate intestinal mucosal inflammation, reinforce the epithelial defense barrier, and modulate visceral sensitivity and intestinal motility. Thus, a deficit in such as

beneficial butyrate -producing bacteria may represent a mechanism of induction of inflammatory disease within the ASD population.

Attention-deficit hyperactivity disorder in children

There is a bidirectional interaction between the gut and the brain termed the gut-brain-axis (GBA), involving the gut microbiome and connecting the peripheral intestinal elements to the central nervous system (CNS). The bidirectional signaling function of microbiota-gut-brain axis is extraordinary, and this interaction between microbiota and intestinal epithelium can cause physiological changes in the brain and influential mood and behavior. Clinical and biological aspects of GBA in attention-deficit hyperactivity disorder (ADHD) is a common childhood-onset psychiatric and neurodevelopmental disorder, which is characterized by having problems with paying attention and/or excessive activity and impulsivity, along with some inflammatory disorders (e.g. asthma, eczema and rhinitis). ADHD is the common behavioral neurodevelopmental disorder estimated to affect approximately 5% of children worldwide. Fan et al^[9] investigated the microbiota by 16S rRNA gene sequencing and short chain fatty acids (SCFAs) concentrations, enrolling 59 ADHD children including 21 inattentive subtypes (ADHD-I), 20 combined subtypes (ADHD-C), 18 hyperactive-impulsive subtypes (ADHD-H) and 23 healthy control. The author exhibited the clinical distinction among different ADHD subtypes in children may be reflected in alterations of specific gut microbiota, most of which are SCFAs producing bacteria. *Faecalibacterium* spp. is suggested as a potential future probiotics due to some strain-dependent anti-inflammatory features, like butyrate production. In the previous review we documented prophylactic roles of butyric acid fermented endophytic bacterial in *Aloe vera* and *A. arborescens* leaves on brain-gut microbiota cooperation in healthy aging^[10]. 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 metabolites, such as butyric acid. Alteration in gut microbiota might be accomplished by altered concentration of SCFAs. Thus interventions that alter the composition of the gut microbiota might reduce pro-inflammatory state and rejuvenate immune functions to produce anticancer and insulin secretion benefits in frail elderly people.

ALTERATION IN SLEEP DISORDER OF CHILDREN WITH AUTISM SPECTRUM DISORDERS

Autism spectrum disorder (ASD) is a type of neurodevelopmental disease that is frequently accomplished by sleep disorder. The autism behavior checklist, social responsiveness scale and childhood autism rating scale were used to assess autism symptoms, and the children sleep habits questionnaire was employed to evaluate sleep problems in children with ASD. ASD children with sleep disorder exhibited declines in the abundance of *Faecalibacterium* and *Agathobacter*, decreased levels of 3-hydroxybutyric acid and melatonin, and an increase in serotonin. The changes may aggravate sleep problems and core symptoms in children with ASD^[11].

A METABOLITE OF INTESTINAL BACTERIA, BUTYRATE, ENHANCES SLEEP

Szentirmal et al^[12] tested the hypothesis that butyrate may serve as a

bacterial-derived sleep- promoting signal. Oral gavage administration of tributyrin, a butyrate pro-drug, elicited an almost 50% increase in non-rapid-eye movement sleep (NREMS) in mice for 4 h after the treatment. Similarly, intra-portal injection of butyrate led to prompt and robust increases in NREMS in rats. In the first 6 h after the butyrate injection, NREMS increased by 70%. Both the oral and intra-portal administration of butyrate led to a significant drop in body temperature. Systemic subcutaneous or intra-peritoneal injection of butyrate did not have any effect on sleep or body temperature. The results suggested that the sleep-inducing effects of butyrate are mediated by a sensory mechanism located in the liver and/or in the portal vein wall.

The relationship between gut microbiota changes and increased inflammatory cytokines in insomnia patients

Li et al^[13] investigated the changes in gut microbiota composition and inflammatory cytokines production associated with acute and chronic insomnia. The gut microbiomes of insomnia outpatients with acute and chronic insomnia compared with healthy controls were characterized by lower microbial richness and diversity, depletion of anaerobes, and SCFA-producing bacteria, and an expansion of potential pathobiont, *Lachnospira* and *Bacteroides* were signature bacteria for distinguishing acute insomnia patients from healthy controls, while *Faecalibacterium* and *Blautia* were signature bacteria for distinguishing chronic insomnia patients from healthy controls. Acute/chronic insomnia-related signature bacteria also showed correlation with these patients' self-reported sleep quality and plasma IL-1 β . The findings suggested that insomnia symptomology, gut microbiota, and inflammation may be interrelated in complex ways. Gut microbiota may serve as an important indicator for auxiliary diagnosis of insomnia and provide possible new therapeutic targets in the field of sleep disorders.

Association between fecal short chain fatty acids and sleep continuity in adults with insomnia symptoms

Exploration of the association between SCFAs and sleep continuity and the comparison SCFAs concentration in short vs. normal sleep insomnia phenotypes in older adults were demonstrated by Magzal et al^[14]. High concentrations of acetate, propionate, butyrate, and total SCFAs were associated with lower sleep efficacy and longer sleep onset latency (SOL) after controlling for body mass index (BMI). Concentrations were high in the short sleep duration phenotype. Age, BMI, total sleep time, and SOL explained 40.7% of the variance in total SCFAs. The findings contributed to understanding pathways along the gut-brain axis and may lead to the use of SCFAs biomarkers of insomnia phenotypes.

INTERACTION OF SODIUM BUTYRATE AND THYROID HORMONE ON GUT-THYROID-AXIS

Enterocyte differentiation is known to be regulated by a variety of extracellular compounds, among which is triiodothyronine (T3) and short chain fatty acids (SCFAs). Because several SCFAs are known to induce histone hyper-acetylation, and T3 action has been recently linked to chromatin structure. Meng et al^[15] investigated the interplay between SCFAs and T3 in regard to the enterocyte differentiation marker, intestine alkaline phosphatase (IAP). Caco-2 cells were treated with 5 mmol/L SCFAs with/without 10 nmol/L T3. Reporter gene activity was measured and the level of histone acetylation assessed by means of acid-urea-triton (AUT) gel assays.

Concomitant treatment with T3 and butyric acid produced an additive effect on IAP gene activation. AUT gel studies demonstrated histone hyper-acetylation in response to SCFA treatment. T3 and butyric acid can act in concert to induce IAP gene transcription, demonstrating an important link between T3 and histone hyper-acetylation in regard to enterocyte-specific gene expression. Effects of butyrate on nuclear-thyroid hormone receptors and on thyroid hormone-responsive nuclear protein were investigated by Nishi et al^[16] by means of a perfusion system in rat liver. Treatment with 5 mM butyrate resulted in an increase in the maximal binding capacity of T3 nuclear receptors without altering the affinity of receptor for T3. However, further perfusion for 4 h decreased the number of the receptors to the control level. Butyrate increased the amount of acetylated histone H4. The ability of nuclear T3 receptors to bind to core histones was diminished by acetylation of core histones. Thyroid hormone-responsive nuclear protein (n protein) was increased by T3. The induction of the n protein by T3 was augmented by butyrate. The results suggested that butyrate modulates thyroid hormone-responsive gene expression in rat liver via the increased number of nuclear receptors or changes in the chromatin constitution.

GUT-BUTYRATE ASSOCIATION WITH PRIMARY HYPOTHYROIDISM WITH INTERACTION ON GUT-THYROID-AXIS

Gut microbiome is associated with thyroid diseases, including Graves's disease, Hashimoto's disease, thyroid nodules, and thyroid cancer. Su et al^[17] characterized gut microbiome in primary hypothyroidism patients. Fifty-two primary hypothyroidism patients and 40 healthy controls were recruited. The differences in gut microbiota between the two groups were analyzed by 16S rRNA sequencing technology. Fecal microbiota transplantation (FMT) was performed in mice using flora from both groups; changes in thyroid function were then assessed in the mice. The SCFAs producing ability of the primary hypothyroidism patients' gut was significantly decreased, which resulted in the increased serum lipopolysaccharide levels. The FMP showed that mice receiving the transplant from primary hypothyroidism patients displayed decreased total thyroxine levels. The findings could help understand the development of primary hypothyroidism and might be further used to facilitate the adjuvant treatment of this disease.

The association with thyroid nodules with gut microbiome alterations

Thyroid nodules are found in nearly half of the adult population, and accumulating evidence suggests that the gut microbiota plays an important role in thyroid metabolism. Li et al^[18] performed a gut microbiome genome-wide association study in 196 patients with thyroid nodules and 283 controls by using whole-genome shotgun sequencing. The gut microbiome in participants with high-grade thyroid nodules is characterized by greater amino acid degradation and low butyrate production. The relative abundances of multiple butyrate producing microbes are reduced in patients with high-grade thyroid nodules and the relative abundances of L-histidine metabolism pathways are associated with thyrotropin-releasing hormone. The study described the gut microbiome characteristics in thyroid nodules and a gut-thyroid link and highlight specific gut microbiota as a potential therapeutic target to regulate thyroid metabolism. And the author showed that the key gut microbiome-driven metabolic pathways, such as butyrate formation, were associated with the presence of thyroid nodules.

CASE REPORTS

Improvement of menopausal symptoms in 48-years old female

A ~40 years old female who had stillbirth of 8 month in her 25-year, had an inflammation of the uterus (the endometrium) resulting in treatment of infertility. Furthermore, she had the treatment to stop menstruation two times during 6 months. After the treatment she spent several years without an illness to worsen. On 48-years old she had a severe menopausal symptoms and she started daily ingestion of aloe vera juice (AVJ) 100ml/day for 3 months. She had a complete remission and no menstrual pain, and a nice well QOL at age 61.

Improvement of chronic headache disorder; so-called migraine in 48-years old female

A 50-years old female who had headache since her childhood, suffered from her overwork and weather condition. She took commercial headache medicine and diagnosed several medicines in hospital at 48-years old. However, she had severe headache and then, she started daily AVJ ingestion. After the ingestion of AVJ 50ml/day for 7-years, she remitted headache without taking dietary supplement. She has a nice and well QOL without any common cold symptoms at age 55.

Improvement of otitis media and sinusitis in 13-years old male

A 10-years old male had been catch cold, otitis media and high fever since three years old. To otitis media treatment he had myringotomy. He had several times of nebulizer treatment during ten years, but had no remission. He could not hear low sound and had aeration treatment. On 13-years old he started to ingest AVJ 100ml/day with some health supplement. After 3 months ingestion of AVJ, he suddenly had a large amount of runny nose. Since then he got a nice sensitivity in nose. And he had no cough and fever symptoms and has a nice well QOL.

Remission of chronic inflammatory demyelinating polyneuropathy (CIDP) in 53-years old male.

A 53-years old male patient caused by too much stress was diagnosed as an intractable disease; CIDP on 2009. He could not move and was bedridden and injected immuno-globulin (400mg/kg/day) for 5 days, but he could not move at all and hospitalized. He was administrated predonin (prednisolone tablet, 40mg/day), immunosuppressant mezopirin (50mg, 2-times/day). He had started to successive ingestion of AVJ 100ml, 3-times/day, on 2008 and he had not moon phase (one of the common but harmless side effects of steroid drug) on October, 2009. He continued to take immuno-globulin 400mg/kg/day for 5 days, at the intervals of 2-weeks. He finally could move on the beginning of 2010. Then he administered immune-globulin 1000mg/kg/day at the intervals of 3-months for half-year. Finally, he had remission on August 2019 and has a nice well QOL and started to play sport without any disease recurrence.

DISCUSSION OF CASE REPORTS

Aloe vera juice (AVJ) is an excellent supplement to regulate menses and reduce excess weight. It is also enhances metabolism and keeps gut system healthy in case report 1. AVJ ingestion helps to correct hormonal imbalance and treat menstrual irregularities, causing poor sleep, depressed mood and vasomotor symptoms. In the previous paper we described that AVJ has both cholesterol-lowering properties and an anti-inflammatory effect. And the effects of a dietary supplementation of AVJ with L-arginine to chronic

fatigue syndrome were demonstrated in the questionnaire to adult subjects^[19]. Furthermore, Dr. Fayyaz Ahmed who is a medical trustee of the Migraine Trust recommended using AVJ as a treatment for headache and migraine. In case report 2 AVJ possibly relieves chronic fatigue syndrome and may remit the migraine. Earaches are common among young children. Abnormalities in the ear can lead to inflammation, swelling and itchiness. Because of the nebulizer treatments several times in case report 3, he had some trouble on the eardrum. The successive AVJ ingestion may help to correct these abnormalities. In case report 4, a CIDP patient's medication record shows as follows: On 2009: immunosuppressant; mezopirin 50mg, 2-times/day. predonin (prednisolone tablet) 40mg/day. On 2011: predonin, 5mg/day. On 2015: predonin, 4mg/day, on 2015: predonin, 1mg/day. On 2020 no predonin administration; AVJ ingestion record: Start on 2008, 100ml, 3-times/day and continued to 2022. The doctor recognized that successive ingestion of AVJ exhibited the mitigation and withdrawal of steroid drug in CIDP patient. In our previous paper, we described the risk-remission for steroid-induced osteonecrosis of femoral head after nephrotic kidney syndrome in child with successive ingestion of AVJ^[20].

Long-successive ingestion of AVJ may help to modulate the immuno-sensitivity via mitigation of pathogenesis and provide high concentration of butyrogenic microbiome in the host gut.

SUMMARY

The importance of the gut-brain axis in maintaining homeostasis has long been appreciated. We discussed the current knowledge focusing on the influence of butyrate fermented in aloe vera gel by which the gut-microbiota is beneficial for brain and behavior to be homeostasis. With the support of the fermented metabolites, human might have been built up a biological defense system such as immunity. Furthermore, we described the role of aloe vera juice (AVJ) successive ingestion to neurological homeostasis in case reports 1-3. It was suggested that AVJ successive ingestion provides an important role not only the drug deprivation (steroid drug withdrawal) but also butyrate fermentation in case report 4.

ACKNOWLEDGEMENT

The authors express deep appreciation for Mr. A Mukaitani, a Chair person of Japan Aloe Science Association to set up case reports.

REFERENCE

1. Al-Madboly LA, Kabbash A, Yassin AM, Yagi A. Dietary cancer prevention with butyrate fermented by Aloe vera gel endophytic microbiota *J. of GHR* 2017; 6(2): 2312-2317 [DOI: 10.17554/j.issn.2224-3992.2017/06.698]
2. A Yagi, M Hasegawa, S Ataka. Prophylactic role of aloe components, butyrate fermented, micrinas, 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]
3. Lindstad LJ, Lo G, Leivers S, Lu Z, Michalak L, Pereira GV, Rohr AK, Martens EC, McKee LS, Louis P, Duncan SH, Westereng B, Pope PB, La Rosa SL. Human gut *Faecalibacterium prausnitzii* develops a highly efficient conserved system to cross-feed on β -mannan-derived oligosaccharides *mBio*. 2021;12(3):e0362820 [DOI: 10.1128/mBio.03628-20]
4. Yagi A, Kabbash A, Al-Madboly LA. Short chain fatty acids from fermentation 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]
5. A Yagi, M Hasegawa, M Mikami, S Ataka. Epigenetic roles of short chain fatty acids as beneficial modulators in the neuroendocrine system case reports: Influence of aloe vera juice to brain homeostasis *J. of GHR* 2021;10(5):3571-2576 [DOI: 10.17554/j.issn.2224-3992.2021. 10.1021]
6. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, Chen TJ, Bai YM. Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: A nationwide population-based study *Res in Autism Spectrum Disorders* 2013;7(2): 205-212 [DOI: 10.1016/j.rasd.2012.08.008]
7. Liu S, Li E, Sun Z, Fu D, Duan G, Jiang M, Yu Y, Mei L, Yang P, Tang Y, Zhang P. Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder *Scientific Reports* 22 January 2019 [DOI:10.1038.s41598-018-36430-z]
8. Cao X, Liu K, Liu J, Liu YW, Xu L, Wang H, Zhu Y, Wang P, Li Z, Wen J, Shen C, Li M, Nie Z Kong XJ. Dysbiotic gut microbiota and dysregulation of cytokine profile in children and teens with autism spectrum disorder *Front. Neurosci.* 10 February 2021 [DOI: 10.3389/fnins. 2021.635925]
9. Fan C, Li S, Wang R, Fan X, Liang A, Qi K. Short chain fatty acids producing bacteria shape the subtype of ADHD in children *Research Square* 2019, Oct.22nd. [DOI: 10.21203/rs.2.16337/v]
10. 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(11): 2896-2901 [DOI: 10.17554/j.issn.2224-3992.2019.8.836]
11. Hua X, Zhu J, Yang T, Guo M, Li Q, Li T. The gut microbiota and associated metabolites are altered in sleep disorder of children with autism spectrum disorders *Front Psychiatry* 2020;11: 855 [DOI: 10.3389/fpsy.2020.00855]; [PMID: 32982808]
12. Szentirmal E, Millican NS, Masie AR, Kapas L. Butyrate, a metabolite of intestinal bacteria, enhances sleep *Sci Rep.* 2019; 9(1): 7035 [DOI: 10.1038/s41598-019-43502-1]
13. Li Y, Zhang B, Zhou Y, Wang D, Liu X, Li L, Wang T, Zhang Y, Jiang M, Tang H, Amsel LV, Fan F, Hoven CW. Gut microbiota changes and their relationship with inflammation in patients with acute and chronic insomnia *Nature and Science of Sleep* 2020;12; 895-905
14. Magzal F, Even C, Haimov I, Agmon M, Asraf K, Shochat T, Tamir S. Associations between fecal short-chain fatty acids and sleep continuity in older adults with insomnia symptoms *Sci Reports* 2022; 22: 4952 [DOI: 10.1038/s41598-021-83389-5]
15. Meng S, Wu JT, Hodin RA. Short-chain fatty acids and thyroid hormone interact in regulating enterocyte gene transcription *Surgery* 1999;126(2):293-298 [PMID: 10455897]
16. Nishi Y, Ichikawa K, Miyamoto T, Takeda T, Kobayashi M, Suzuki S, Sakurai A, Hashizume K. n-Butyrate enhances induction of thyroid hormone-responsive nuclear protein *Endocrine J.* 1993; 40(5): 515-521
17. Su X, Zhao Y, Li Y, Ma S, Wang Z. Gut dysbiosis is associated with primary hypothyroidism with interaction on gut-thyroid axis *Clin Sci (London)* 2020; 134(12): 1521-1535 [DOI: 10.1042/CS20200475]
18. Li A, Li T, Gao X, Yan H, Chen J, Huang M, Wang L, Yin D, Li H, Ma R, Zeng Q, Ding S. Gut microbiome alterations in patients with thyroid nodules *Front. Cell. Infect. Microbiol.* 2021;12 March [DOI: 10.3369/fcimb.2021.643968]
19. A Yagi and 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]
20. K Koizumi, M Hasegawa A Mukaitani, A Yagi. Case reports: Beneficial roles of aloe vera juice-successive ingestion to children with steroid-sensitive nephrotic syndrome *J. of GHR* 2020 9(1): 3093-3095 [DOI: 10.17554/j.issn.2224-3992.2020.09.893]