

Prophylaxis Role of Kampo- and Diagnosed-Drug with Butyrate Fermented in Aloe Vera Gel as an Adjuvant for Mitigating and Relieving Pain in Spinal Stenosis and Restoring of Osteoporosis

Yagi Akira^{1*}, Hasegawa Megumi² and Shiba Kosuke³

¹Special Advisor of Japan Aloe Science Association, Professor Emeritus of Fukuyama University, Hiroshima, Japan

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

³A Clinical Director of Medical Association and Occupational Physician, Yokohama-City, Kanagawa-ken, Japan

***Corresponding Author:** Yagi Akira, Special Advisor of Japan Aloe Science Association, Professor Emeritus of Fukuyama University, Hiroshima, Japan.

Received: October 09, 2023; **Published:** October 19, 2023

Abstract

Case Report 1: A 42-years old male, 190 cm height-veterinarian in Hokkaido who had a heavy hard work in winter, can't move from his work, and diagnosed spinal stenosis on 2020. Then, he took painkiller drug, but still suffering from a waist pain. He started to take Kampo-drug: Sokei-kakketsuto with Aloe vera juice (AVJ) 200 ml/d on July 2021. During July to September he had mitigated a waist pain, and completely recovered with taking the Kampo-drug with AVJ for 5-months at the end of January, 2022. He had a well-being without the Kampo drug and pain, and is well-working on September, 2023.

Case Report 2: An 80-years old male who had side effect of Corona vaccination, suffered from heavy pyrexia and muscle pain, and had been in bed for 10 days on July, 2021. He diagnosed spinal stenosis and ingested a pain killer drug; Loxoprofen sodium hydrate, and started to walk for rehabilitation. Then, he started to drink AVJ 200 ml/d without the drug and continued rehabilitation and had well-being running and swimming without a waist pain on September, 2023.

Case Report 3: An 89-years-old male who diagnosed Radium-223 chloride (an inhibitor of bone metastasis: Xofigo) as an investigation new intravenous injection and castration-resistant prostate cancer drug (enzalutamide), every one month from August, 2022. After one year investigation, he had a well-QOL, no side effect and inhibition of prostate cancer and bone metastasis on September, 2023. During ten years after his retired the work, he had used to ingest AVJ 100 ml/d. Now he takes enzalutamide with AVJ and small walking on sunny day and has a well-being QOL on October, 2023.

Case Report 4: A 60-years old female fell off her bicycle her left arm on June, 2015. Her bone mineral density (BMD) was examined 88% comparing to bone density reference value (BDRV) in the same years old-female. She did not to take the drug and drink to start only AVJ 150 ml/d on July 2015. Then, her BMD was recovered to 95% BDRV on September, 2016. Furthermore, she only continued to drink AVJ 180 - 200 ml/d and she recovered BMD 106% and the doctor diagnosed complete cure of osteoporosis on July, 2018.

Keywords: Kampo-Drug; Butyrate; Aloe Vera Gel; Spinal Stenosis; Osteoporosis

Introduction

Microbial metabolites are known to modulate immune responses of the host, and the short chain fatty acids affect local and systemic immune functions. In the previous paper [1], we demonstrated that the inner leaf gel of Aloe vera leads to fermentation with endophytic bacteria, such as *Bacillus cereus*, *B. licheniformis*, and *Lactobacillus paralimentarium*, providing butyric acid by GC/MSD analysis from ether extract of gel fermentation broth.

Furthermore, two case reports [2] suggested the successive ingestion of aloe vera juice provided high concentration of butyrogenic microbiome *Faecalibacterium* spp. in fecal, and could play a beneficial role for tissue repair and bone regeneration. In autoimmune arthritis, traditionally classified as a T helper (Th) type 1 disease, the activation of T cells resulted in bone destruction mediated by osteoclasts, but how T cells enhance osteoclastogenesis despite the anti-osteoclastogenic effect of interferon (IFN)- γ remains to be elucidated. Sato, *et al.* [3] examined the effect of various Th cell subsets on osteoclastogenesis and identified Th17, a specialized inflammatory subset, as an osteoclastogenic Th cell subset that links T cell activation and bone resorption. The interleukin (IL)-23-IL-17 axis, rather than the IL-12- γ axis, is critical not only for the onset phase, but also for the bone destruction phase of autoimmune arthritis. Thus, the author determined that Th17 is a powerful therapeutic target for the bone destruction associated with T cell activation. Tyagi, *et al.* [4] examined the impact of supplementation with *Lactobacillus rhamnosus* GG (LGG) on bone homeostasis in estrogen-deficient young mice. Butyrate produced in the gut following LGG ingestion, or butyrate fed directly to germ-free mice induced the expansion of intestinal and bone marrow (BM) regulatory T (Treg) cells. Interaction of BM CD8⁺ T cells with Treg cells resulted in increased secretion of Wnt10b, a bone anabolic Wnt ligand. Mechanistically, Treg cells promoted the assembly of a NFAT1-SMAD3 transcription complex in CD8⁺ T cells from Wnt 10b^{-/-} mice, prevented butyrate-induced bone formation and bone mass acquisition. Thus, butyrate concentrations regulate bone anabolism via Treg cell-mediated regulation of CD8⁺ T Wnt 10b production.

In the present case reports 1 and 2, we described the positive role of Kampo drug and Loxonin, respectively, in mitigating and relieving pain in a spinal canal stenosis with butyrate fermented with endophytic bacteria in Aloe vera gel as an adjuvant. In case report 3, we described the inhibition of bone metastasis with ²²³Ra (Xofigo) as an investigation new intravenous injection every month and enzalutamide (castration-resistant prostate drug) with AVJ ingestion as an adjuvant. In case report 4 we exhibited the cure of osteoporosis with long time ingestion of AVJ.

Postmenopausal bone loss related to gut microbiota

Takimoto, *et al.* [5] investigated the treatment effect of the probiotic *Bacillus subtilis* C-3102 (C-3102) on bone mineral density (BMD) and its influence on gut microbiota in healthy postmenopausal Japanese women. Seventy-six healthy postmenopausal Japanese women were treated with a placebo or C-3102 spore-containing tablets for 24 hours. The relative abundance of genus *Bifidobacterium* significantly increased at 12 weeks of treatment compared with the baseline in the C-3102 group. The relative abundance of genus *Fusobacterium* was significantly decreased in the C-3102 group at 12 and 24 weeks of treatment compared with the baseline. These data suggest that C-3102 improves BMD by inhibiting bone resorption and modulating gut microbiota in healthy postmenopausal women.

Faecalibacterium prausnitzii is a representative bacterium that produces butyrate and this microbe exerts anti-inflammatory effects in autoimmune disease, such as rheumatoid arthritis

Moon, *et al.* [6] showed a therapeutic effect on rheumatoid arthritis (RA) by *Faecalibacterium* (F.) *prausnitzii* administered in a mouse model of RA. In addition, administration of *F. prausnitzii* reduced the abundance of systemic immune cells that secrete the pro-inflammatory cytokine IL-17 and induced changes in short chain fatty acids (SCFAs) concentrations and the intestinal microbial flora composition. It also resulted in decreased lactate and acetate concentrations, an increased butyrate concentration, and altered compositions of bacterial

known to exacerbate or improve RA. The results suggested that *F. prausnitzii* exerts a therapeutic effect on RA by regulation of IL-17 producing cells. And *F. prausnitzii* modified the microbial flora composition and SCFAs in experimental RA mouse model.

Short chain fatty acids affect local and systemic immune functions and regulate osteoclast metabolism and bone mass *in vivo*

Lucas., *et al.* [7] investigated that short chain fatty acids (SCFA) are regulators of osteoclast metabolism and bone mass *in vivo*. Treatment of mice with SCFA as well as feeding with a high-fiber diet significantly increases bone mass and prevents postmenopausal and inflammation-induced bone loss. The protective effects of SCFA on bone mass are associated with inhibition of osteoclast differentiation and bone resorption *in vitro* and *in vivo* while bone formation is not affected. Mechanistically, propionate and butyrate induce metabolic reprogramming of osteoclast resulting in enhanced glycolysis at the expense of oxidative phosphorylation, thereby downregulating essential osteoclast gene such as TRAF6 and NFATc1. The data identified SCFAs as potent regulators of osteoclast metabolism and bone homeostasis.

Mechanisms of gut microbiota-mediated bone remodeling

Yan., *et al.* [8] demonstrated that gut microbiota influence bone remodeling distally, promoting both bone resorption and formation. The author proposed that these effects are mediated, at least in part, by the induction of insulin like growth factor by the microbiota metabolite short chain fatty acids (SCFA). The author explored additional mechanisms by which microbial metabolites could directly or indirectly alter host bone remodeling. And the author discussed whether SCFA directly modulate bone resorption by their actions on osteoclasts, and tested the possibility that serotonin is another gut microbiota derived long-distance mediator of effect on bone remodeling. The author suggested that a detailed understanding of the mechanisms of microbiota effect on bone remodeling could help establish potential therapeutic strategies to promote bone health.

Short chain fatty acids play a key role in the pathogenesis of neuropathic pain by regulating microglial activation and subsequent pro-inflammatory phenotype polarization

Zhou., *et al.* [10] demonstrated that chronic construction injury (CCI) was used to induce neuropathic pain in mice. And the mechanical withdrawal threshold and thermal hyperalgesia were accomplished. The results suggested that CCI can lead to mechanical and thermal hyperalgesia, while short chain fatty acids (SCFAs) play a key role in the pathogenesis of neuropathic pain by regulating microglial activation and subsequent pro-inflammatory phenotype polarization. The author suggested that SCFAs highly participated in the development of neuropathic pain, possibly via hippocampal and spinal microglia polarization mediated neuroinflammation. Thus, it was provided that the potential molecular mechanisms underlying SCFAs, such as butyric acid, mediated neuropathic pain as gut-brain axis.

Case Report 1

A 42-years old 190 cm height male veterinarian in Hokkaido who had a heavy work in winter, can't move from his hard work, and diagnosed spinal stenosis on 2020. He took a pain killer drug, but still suffered from a waist pain. Then, he started to take Kampo pain killer drug, Sokei-kakketsuto with Aloe vera juice (AVJ, 200 ml/d) as an adjuvant on July 2021. During July to September 2021, he had mitigated a waist pain and completely recovered with the Kampo-drug and AVJ ingestion for 5-months by the end of January, 2022. He is a well-being without Kampo-drug and a waist pain, and is well working on September, 2023.

Case Report 2

An 80-years-old male who had side effect of Corona vaccination, suffered from heavy pyrexia and muscle pain, and had been in bed for 10-days on July, 2021. He diagnosed spinal stenosis and took a pain killer drug: Loxoprofen sodium hydrate (Loxonin), and started to walk for rehabilitation. Then, he started to ingest AVJ 200 ml/d without the drug and continued rehabilitation and has well-being with running and swimming without a waist pain on September, 2023.

Case Report 3

An 89-years old male, who had castration-resistant prostate cancer, diagnosed Radium-223 chloride (Xofigo) as an investigation new an intravenous injection for bone metastasis every one month for one year and castration-resistant prostate cancer drug (enzalutamide) from August, 2022. After one year investigation, he had a well-QOL, no side effect and inhibition of castration-resistant prostate cancer and bone metastasis. During ten years after he retired the work, he used to ingest AVJ 100 ml/d. He takes anti-prostate drug with AVJ as an adjuvant and small walking on sunny day and has a well-being QOL on October, 2023.

Case Report 4

A 60-years-old female fell off her bicycle her left arm on June 2015. Her mineral density (BMD), 88%, comparing to the same years-female, was diagnosed osteoporosis. She took only AVJ 150 ml/d without the drug, July, 2015. Then, the BMD value recovered to 95% bone density reference value of the same years-old female on September, 2015. Furthermore, she continued to drink AVJ 180-200ml/d. and recovered her BMD 105% and the doctor diagnosed complete cure of osteoporosis on 2018.

Discussion for Case reports

In previous case report [2], we showed the successive ingestion of aloe vera juice ingestion provided high concentration of the butyrogenic microbiome *Faecalibacterium* spp. in fecal and could play a beneficial role for tissue repair and bone regeneration. Furthermore, we [9] discussed the role of acemannan and hyaluronan in Aloe vera gel for inflammatory wound healing and recovery of bone and the case reports recovering to bone mineral density and regeneration. Present case report 1-2 showed patients with spinal stenosis completely recovered with Kampo-drug and Loxonin with AVJ as an adjuvant. In case report 1, Kampo-pharmacist Hasegawa supposed that the 190 cm high veterinarian who had a heavy work may be suffered from spinal stenosis in cold winter season in Hokkaido. Then, she prescribed Kampo-drug Sokei-Kakketsuto with AVJ as an adjuvant. And the veterinarian had well QOL.

The side effect of Corona vaccination is very severe problem in elder person having preexisting underlying diseases. In case report 2, 80-years old male patient with side effect of covid vaccination diagnosed spinal stenosis recovered waist and muscle pain with the waist killer loxonin with AVJ as an adjuvant. He had well-QOL after ingesting AVJ without loxonin.

In case report 3, an 89-years old male having castration resistant prostate cancer and bone metastasis patient, diagnosed enzalutamide and Radium 223 (Xofigo). And he had a well QOL after the treatment of the new investigation of intravenous injection for one year from August, 2022. He had the prostate cancer drug and the intravenous injection with AVJ as an adjuvant, and has a small walking on sunny day, and a well-being QOL on October, 2023.

In case report 4, a 60-years-old female patient having an osteoporosis was completely cured with AVJ ingestion for three-years.

Originally, we have several case reports showing AVJ-ingestion recovered bone mineral density (BMD), but did not have the before/after data of BMD in the patients, because they did not visit the kampo-pharmacy after recovered osteoporosis with AVJ ingestion, and we presented only one before/after comparing BMD data in case report-4, in osteoporosis patient. Now, she has a well-being QOL on October, 2023.

Summary

Bone spurs in over age 50 and effects of butyrate on bone health were discussed. The bone spurs can push into the spinal canal. Most spinal stenosis occurs when the reduction of the amount of open space within the spin. Disks are the soft cushions that act shock absorbers between spinal bones. Most people with spinal stenosis are over age 50 and case report 1 and 2, provided evidence indicating the potential molecular mechanisms underlying SCFAs mediated neuropathic pain in spinal stenosis. In case report 3, an 89-years-old

male castration-resistant prostate cancer patient, diagnosed Xofigo for one year. And he had castration-resistant prostate cancer drug with AVJ ingestion and a well-being QOL after the treatment of Xofigo without any side effect and a bone metastasis. And case report-4 exhibited cure of osteoporosis with AVJ ingestion for 3-years.

Present reviews indicated that the prophylaxis role of microbial metabolite butyrate, fermented in Aloe vera gel as an adjuvant, modulates bone-homeostasis formation.

Bibliography

1. A Yagi., *et al.* "Short chain fatty acids from fermentation by endophytic bacteria in Aloe vera leaf rind and gel". *Journal of Gastroenterology and Hepatology Research* 5.4 (2016): 2122-2124.
2. A Yagi., *et al.* "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 Ale vera juice ingestion producing intestinal butyrogenic microbiome and bone regeneration". *Journal of Gastroenterology and Hepatology Research* 10.1 (2021): 3398-3406.
3. Sato K., *et al.* "Th17 functions as an osteo-clastogenic helper T cell subset that links T cell activation and bone destruction". *Journal of Experimental Medicine* 203.12 (2006): 2673-2682.
4. Tyagi AM., *et al.* "The microbial metabolite butyrate stimulates bone formation via T regulatory cell-mediated regulation of WNT10B expression". *Immunity* 49.6 (2018): 1116-1131.e7.
5. Takimoto T., *et al.* "Effect of *Bacillus subtilis* C-3102 on bone mineral density in healthy postmenopausal Japanese women: a randomized, placebo-controlled, double-blind clinical trial". *Bioscience of Microbiota, Food and Health* 37.4 (2018): 87-96.
6. Moon J., *et al.* "*Faecalibacterium prausnitzii* alleviates inflammatory arthritis and regulates IL-17 production, short chain fatty acids, and the intestinal microbial flora in experimental mouse model for rheumatoid arthritis". *Arthritis Research and Therapy* 25.1 (2023): 130.
7. Lucas S., *et al.* "Short chain fatty acids regulate systemic bone mass and protect from pathological bone loss". *Nature Communications* 9.1 (2018): 55.
8. Yan J., *et al.* "Mechanisms of gut microbiota-mediated bone remodeling". *Gut Microbes* 9.1 (2018): 84-92.
9. A Yagi., *et al.* "Putative roles of Aloe vera gel and inflammatory process: Case reports of bone mineral regeneration, and regression of mesenteric lymphadenopathy and microscopic polyangiitis". *Journal of Gastroenterology and Hepatology Research* 10.3 (2021): 3537-3539.
10. Zhou F., *et al.* "Short-chain fatty acids contribute to neuropathic pain via regulating microglia activation and polarization". *Molecular Pain* 17 (2021): 1744806921996520.

Volume 6 Issue 11 November 2023

©All rights reserved by Yagi Akira., *et al.*