

## The Association of Butyrate Fermented in Aloe Vera Gel with Bone and Muscle Generation Case Reports: Recovery of Dermatologic Microscopic Polyangiitis with Kampo Medicine and Aloe Vera Juice (AVJ), and Beneficial Role of AVJ to Migraine and Movement

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### ABSTRACT

Regeneration of muscle and bone with *Aloe vera* gel and fermented butyrate in *Aloe vera* gel in clinical fields were reviewed based on gut-bone axis. Beneficial roles of butyrate fermented in aloe vera gel on the regeneration of bone and muscle were widely expressed. In case reports regeneration of dermatologic microscopic polyangiitis

with kampo medicine and aloe vera juice (AVJ), and beneficial role of AVJ to migraine and movement were demonstrated.

**Key words:** Aloe vera gel; Butyrate fermented; Bone and muscular regeneration; Case reports

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### INTRODUCTION

*Aloe vera* gel is a rich source of antioxidant, which helps fight free radicals. This lowers oxidative stress on human body and reduces the risk of chronic conditions such as diabetes and heart disease. *Aloe vera* gel is an excellent source of vitamin C, Ca<sup>2+</sup>, and Mg<sup>2+</sup>. Mg<sup>2+</sup> helps human body with enzyme reactions, including those that regulate the body pressure and the heart rhythm. Acemannan (ACM), primary freeze dried polysaccharide of *Aloe vera* inner gel has been shown to stimulate pulpal fibroblasts, gingival fibroblasts, and cement-blasts in the dental field study. Gonna et al<sup>[1]</sup> suggested that ACM sponge may be a suitable agent for pulpotomy in primary teeth, and the inflammatory response was less severe and no necrosis was noted after pulpotomy with ACM compared to formocresol (the most widely used medicament for pulpotomized primary teeth). Furthermore, Gonna et al<sup>[2]</sup> demonstrated that ACM showed higher clinical and radiographic success rate compared to formocresol as a pulpotomy agent in molars<sup>[3,4]</sup>. ACM was possibly considered as an acceptable biomarker for vital pulp therapy of deep caries in primary teeth. In previous paper we showed that nutraceutical *Aloe vera* gel

scaffolds, such as ACM, promote soft tissue organization in biomedical applications and polymeric matrix. ACM scaffolds showed the possible improvement of knee joint comfort and flexibility for supporting a healthy muscle movement. ACM has the efficacious roles in amelioration of human diseases, such as skeletal bone and muscle sarcopenia. In the previous paper, fermentation by endophytic bacteria in *Aloe vera* inner gel provided short chain fatty acid, butyric acid<sup>[5]</sup>. Daily intake of *Aloe vera* gel may provide the possible potential preventive roles in human health. The role of active constituents and butyrate fermented from *Aloe vera* gel was discussed on the basis of gut microbiota-gut axis<sup>[6]</sup>.

In present report we discussed the roles of *Aloe vera* juice (AVJ) ingestion, butyrate fermented, and oral hyaluronan ingestion for inflammatory muscle healing and recovery of bone. In two case reports we described the recovery of dermatologic microscopic polyangiitis with Kampo medicine and AVJ (prednisolone withdrawal), and the beneficial role of AVJ to migraine and movement.

## ASSESSMENTS OF HUMAN AND RAT CLINICAL PARAMETERS OF ALOE VERA GEL IN RHEUMATOID ARTHRITIS

The possibility of *Aloe vera* gel in the treatment of rheumatoid arthritis (RA) by evaluating experimental arthritic conditions-rat induced by Freund's complete adjuvant was determined by Guha *et al*<sup>[7]</sup>. *Aloe vera* gel extract can be beneficial for the reduction of inflammatory edema and for the reduction of ceruloplasmin in RA condition in rat model. However, further investigations are necessary for more refined therapeutic usage of aloe vera gel for the treatment of RA in human.

### The effect of BMP7 in bone defect tissue healing of treated with Aloe vera gel topical application

Histological and immune-histochemical evaluation for expression of BMP7, a protein that in human is encoded by the BMP7 gene, which play a key role in the transformation of mesenchymal cells into bone, were showed with *Aloe vera* gel. Al-Hijazi *et al*<sup>[8]</sup> exhibited the *in vivo* results suggesting that *Aloe vera* gel could function as a bioactive material inducing bone formation by stimulating proliferation and differentiation of osteoblasts with high expression of BMP7. Putative roles of *Aloe vera* gel juice (AVJ) to bone mineral regeneration in aging and inflammatory processes were reported in previous paper<sup>[9]</sup>.

## PUTATIVE ROLE OF ALOE VERA GEL IN INFLAMMATORY PROCESS

The prevention of membrane lysis and protein denaturation in the presence of *Aloe vera* gel homogenate up to the concentration of 1000mg/ml of gel has been assessed *in vitro* by Paul *et al*<sup>[10]</sup>. The regulation of expression of inflammation mediator genes (TNF $\alpha$  and Cox-2) has been investigated *in vitro*. The author also investigated the putative role of *Aloe vera* gel by use of Freund's complete adjuvant-induced inflammatory arthritic Wister albino rats in 28-day long study following the daily oral supplementation of *Aloe vera* homogenate doses up to 0.40 and 0.80g/kg body weight. The role of *Aloe vera* gel homogenate in preventing tissue damage and in the downregulation of TNF $\alpha$  and Cox-2 gene expressions for the immune-modulation of inflammatory arthritis condition was justified. Putative role of *Aloe vera* gel ingestion in aging and inflammatory process was discussed and the beneficial roles in bone mineral regeneration, regression

of mesenteric lymphadenopathy, and microscopic angiitis were expressed in our previous paper<sup>[9]</sup>.

### Acemannan increasing bone regeneration of a calvarial defect model in skeletally mature rats

The effect of acemannan (ACM) in calvarial defect healing was investigated by Godoy *et al*<sup>[11]</sup>. Microcomputed tomography (micro CT) and histopathological analysis were demonstrated in a calvarial defect model by ACM. Micro CT revealed a significant increase in bone surface and bone volume in the ACM treated 1mg and 2mg groups, and tissue mineral density in the 4mg and 8mg treated groups compared with the control group. Histologically, ACM-treated groups had denser bone matrix compared with the control group, showing that ACM is an effective agent for bone regeneration enhancing bone growth as assessed in two- and three-dimensions.

## BUTYRATE IMPROVES METABOLISM AND REDUCES MUSCLE ATROPHY DURING AGING

Sarcopenia, the loss of skeletal muscle mass and function during aging, is a major contributor to disability and frailty in the elderly. Beneficial effect of butyrate on muscle mass during aging and butyrate contribution to age-related muscle atrophy were investigated by Walsh *et al*<sup>[12]</sup>. The possible mechanism of butyrate action through induction of beneficial skeletal muscle mitochondrial adaptations was established by Henagan *et al*<sup>[13]</sup>. The relationships between diet quality, the relative abundance of butyrate-producing bacteria of the gut microbiome and muscle mass, strength and function were investigated by Davis *et al*<sup>[14]</sup>. The relative abundance of butyrate-producing bacteria was positively associated with healthier muscle mass, strength and function; however, these relationships were attenuated in multivariable models.

## THE PROTECTIVE EFFECTS OF BUTYRATE ON DIABETIC NEPHROPATHY-INDUCED MUSCLE ATROPHY

Muscle protein catabolism in patients with diabetic nephropathy (DN) results in striking loss of muscle proteins, which increases morbidity and mortality risks. Tang *et al*<sup>[15]</sup> investigated changes in serum butyrate levels in DN patients using metabolomics analyses. Butyrate exerts protective effects on muscle atrophy induced by DN by enhancing intestinal barrier function and activating the free fatty acid receptor-mediated PI3K/Akt/mTOR pathway (a major factor mediating the regulation of muscle protein metabolism). In the obese mice, supplementation of butyrate led to an increase in insulin sensitivity and a reduction in adiposity.

## BUTYRATE IMPROVES INSULIN SENSITIVITY AND REGULATES LIVER MITOCHONDRIA FUNCTION

Dietary supplementation of butyrate can prevent and treat diet-induced obesity and insulin resistance in mouse models of obesity. Gao *et al*<sup>[16]</sup> investigated the mechanism of butyrate action is related to promotion of energy expenditure and induction of mitochondria function. Stimulation of proteasome activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) activity may be a molecular mechanism of butyrate activity. Activation of AMPK (5' adenosine monophosphate-

activated protein kinase) and inhibition of histone deacetylase may contribute to PGC-1 $\alpha$  regulation. Butyrate may have potential application in the prevention and treatment of metabolic syndrome in humans.

The mechanism underlying the effect of butyrate on protecting liver metabolism and its relationship with mitochondrial function was investigated by Mollica *et al*<sup>[17]</sup>. Hepatic mitochondria were identified as the main target of the beneficial effect of butyrate and its synthetic derivative (N-(1-carbamoyl-2-phenyl-ethyl) butyramide, FBA). The shift of the mitochondrial dynamic toward fusion by butyrate and FBA resulted in the improvement not only of mitochondrial cell energy metabolism but also of glucose homeostasis.

## BUTYRATE ENHANCES MITOCHONDRIAL FUNCTION IN A WIDE VARIETY OF CONDITION INCLUDING AUTISM SPECTRUM DISORDERS

Butyrate positively modulates mitochondrial function, including enhancing oxidative phosphorylation and beta-oxidation and has been proposed as a neuro-protectant. Butyrate has been associated with autism spectrum disorders (ASD), condition associated with mitochondrial dysfunction. Rose *et al*<sup>[18]</sup> have developed a lymphoblastoid cell line (LCL) model of ASD, with a subset of LCLs demonstrating mitochondrial dysfunction (AD-A), and another subset of LCLs demonstrating normal mitochondrial function (AD-N). Butyrate was found to modulate individual LCL mitochondrial respiration to a common set-point, with this set point slightly higher for the AD-A LCLs as compared to the other groups. The data showed that the enteric microbiome-derived butyrate modulates mitochondrial activity with this modulation dependent on concentration, microenvironment redox state, and the underlying mitochondrial function of the cell. The result suggested that butyrate can enhance mitochondrial function in the context of physiological stress and/or mitochondrial dysfunction, and may be an important metabolite that can help rescue energy metabolism during disease states.

## THE ACTIVITY OF BUTYRATE TO PREVENT OSTEOPOROSIS

### On the bone and mitochondria connection

Bone is a living tissue that not only mechanically supports the body and protects vital organs, but also produces blood cells, stores minerals and impacts endocrine regulation. As a result of aging, hormonal imbalances, nutrient deficiencies and insufficiencies, or the frequent use of certain medications, bone remodeling cycle may become unbalanced with bone resorption rates outpacing formation. Tang *et al*<sup>[19]</sup> evaluated the activity of sodium butyrate to prevent osteoporosis in rats. Oxidative stress (OS) and mitochondrial dysfunction are key pathophysiological features of osteoporosis and obesity. Sodium butyrate (SB) has been demonstrated to protect against OS by improving specific antioxidant enzymes and to regulate mitochondria redox homeostasis *in vivo*. The author identified femur mitochondria as the main target of the beneficial effects of SB, consisting of reversion of bone loss and body-weight gain in obesity-prone rats. The author showed SB promoting the Nrf2/GSK-3 $\beta$  signaling pathway and mitochondrial function plays a potential therapeutic strategy for obesity and osteoporosis.

## BUTYRATE ALLEVIATES OXIDATIVE STRESS, INTESTINAL EPITHELIUM BARRIER INJURY, AND MITOCHONDRIAL DYSFUNCTION INDUCED BY H<sub>2</sub>O<sub>2</sub> THROUGH AMPK-MITOPHAGY PATHWAY

Li *et al*<sup>[20]</sup> investigated by use of a hydrogen peroxide-induced oxidative stress model to study whether butyrate could alleviate oxidative stress, intestinal epithelium injury, and mitochondrial dysfunction of porcine intestinal epithelial cells (IPEC-J2) in AMPK-mitophagy-dependent pathway. The author found that after interference with AMPK $\alpha$ , the protective effect of butyrate on IPEC-J2 cells treated with H<sub>2</sub>O<sub>2</sub> was suppressed, indicating that AMPK $\alpha$  is necessary for butyrate to exert its protective effect. AMPK: 5'-Adenosin monophosphate-activated protein-kinase. Mitophagy: an evolutionarily conserved cellular process to remove dysfunctional or superfluous mitochondria, thus fine-tuning mitochondria number and preserving energy metabolism.

## THE GUT-BONE AXIS AND IMPLICATIONS OF BUTYRATE TREATMENT ON OSTEO-IMMUNOLOGY

The effects of butyrate on cell proliferation, alkaline phosphatase (ALPase) activity, mineralized nodule formation, extracellular matrix protein expression, macrophage colony-stimulating factor (M-CSF) and osteoprotegerin (OPG) in normal osteoblasts were examined by Katono *et al*<sup>[21]</sup>. Mineralized nodule formation and the calcium content of mineralized nodules were increased by butyrate in a dose-dependent manner. Cell proliferation and ALPase activity were not affected by the addition of butyrate. Following addition of 10<sup>-4</sup> M butyrate, the expression levels of bone sialoprotein (BSP), osteopontin (OPN), and OPG increased, whereas the expression level of type I collagen and M-CSF were not markedly affected. Butyrate stimulated bone formation by increasing the production of BSP and OPN, where it suppressed osteoclast differentiation by increasing the production of OPG by human osteoblasts.

Tyagi *et al*<sup>[22]</sup> showed that oral supplementation with the widely used probiotic, *Lactobacillus rhamnosus* GG (LGG), increases bone mass in mice by increasing the serum levels of the SCFA, butyrate. LGG or butyrate increases the frequency of regulatory T (Treg) cells in the intestine and in the bone marrow. Treg cells stimulate CD8<sup>+</sup> T cells to secrete the Wnt ligand Wnt10b, which stimulates bone formation by activating Wnt signaling in osteoblasts. Therefore, LGG and butyrate may represent new interventions for the prevention and treatment of osteoporosis.

Therapeutic supplementation of short chain fatty acid (SCFA), butyrate or diets, increasing the endogenous production of SCFAs, may provide a powerful instrument to balance osteoclast activity and inhibit bone resorption. In case of inflammatory bone loss the combination of anti-inflammatory immune-regulatory properties of SCFAs together with the direct inhibition of osteoclast activity may be particularly useful. Lucas *et al*<sup>[23]</sup> investigated that SCFAs are regulators of osteoclast metabolism and bone mass *in vivo*. Treatment of mice with SCFA significantly increased bone mass and presented post-menopausal and inflammation-induced bone loss. Mechanistically, propionate and butyrate induced metabolic reprogramming of osteoclasts resulting in enhanced glycolysis at the expense of oxidative phosphorylation, thereby downregulating

essential osteoclast genes such as TNF receptor-associated factor 6 and nuclear factor of activated T cell c1. These data identified SCFAs as potent regulators of osteoclast metabolism and bone homeostasis.

## THE EFFECTS OF SCFAS ON THE MUSCULOSKELETAL SYSTEM AND THE MECHANISMS WHEREBY SCFAS REGULATE BONE CELLS

The gut microbiome is a key regulator of bone health that affects postnatal skeletal development and skeletal involution. One mechanism whereby microbes influence organs of the body is through the production of metabolites that diffuses from the gut into the systemic circulation. SCFAs which are generated by fermentation of carbohydrates complex, have emerged as key regulatory metabolites produced by the gut microbiota. The effects of SCFAs on the musculoskeletal system and the mechanisms whereby SCFAs regulate bone cells were discussed by Zaiss *et al*<sup>[24]</sup>.

## ATTENUATION OF RHEUMATOID INFLAMMATION BY SODIUM BUTYRATE

Rheumatoid arthritis (RA) is a chronic autoimmune disorder demanding the development of novel therapeutic strategy. Butyrate which is one of the major metabolites of gut microbiota exerts an anti-inflammatory effect by activating G-protein-coupled receptors and inhibiting histone deacetylase (HDACs). Kim *et al*<sup>[25]</sup> focused on the inhibition of the HDACs by butyrate in RA. The arthritis score and incidence were lower in the butyrate-treated group compared to the control group. Butyrate inhibited HDAC2 in osteoclasts and HDAC8 in T cells, leading to the acetylation of glucocorticoid receptors and estrogen-related receptors  $\alpha$ , respectively. The findings suggest that butyrate ameliorates rheumatoid inflammation by targeting HDAC2 in osteoclasts and HDAC8 in T cells. Butyrate is a candidate agent for the treatment of RA.

### Inhibition of collagen-induced arthritis with butyrate

To investigate the attenuation of butyrate on rheumatoid arthritis (RA), the collagen-induced arthritis (CIA) mouse model was established and butyrate was administered in drinking water along with the collagen immunization. The histopathological features, clinical score, paw swelling as well as the production of pro-inflammatory cytokines including IL-1 $\beta$ , IL-6, and IL-17A were measured to determine the amelioration of butyrate on arthritis. Mechanism study by Hui *et al*<sup>[26]</sup> revealed that butyrate directly enhanced the polarization of Treg cells but not Th17 cells. All effects of butyrate on rheumatoid arthritis (RA) were inverted by the co-administrated anti-IL10R antibody. The study showed that butyrate administration inhibited arthritis in CIA mice model, suppressed the expression of inflammatory cytokines. The modulation may be mediated the differentiation of CD4 T cells towards Treg cells, which produce anti-inflammatory cytokine IL-10, and thus influenced the function of Th17 cells.

### Limitation of the autoimmune response with microbiota-derived butyrate by promoting the differentiation of follicular regulatory T cells

Follicular regulatory T (T<sub>FR</sub>) cells play critical regulatory roles in the pathogenesis of autoimmune diseases, including RA. Reduced number of circulating T<sub>FR</sub> has been associated with the elevation of

autoantibodies and disease severity in RA. Butyrate mitigated the pathological events by promoting T<sub>FR</sub> cell differentiation. Butyrate directly induced the differentiation of functional T<sub>FR</sub> cells in vitro by enhancing histone acetylation in T<sub>FR</sub> cell marker genes. The effect was attributed to HDAC inhibition by butyrate, leading to histone hyperacetylation in the promoter region of the T<sub>FR</sub> cell marker genes. Accordingly, butyrate serves as an environmental cue to enhance T<sub>FR</sub> cells, which suppress autoantibody production in the systemic lymphoid tissue, eventually ameliorating RA. Takahashi *et al*<sup>[27]</sup> provided mechanistic insight into the link between the gut environment and RA risk.

### Sodium butyrate attenuates osteoarthritis progression by restoring impaired autophagy and autophagy-flux

Osteoarthritis (OA) is a degenerative joint disease with multiple etiologies that affects individuals worldwide. Zhou *et al*<sup>[28]</sup> demonstrated that sodium butyrate (SB) attenuated OA progression, including the amelioration of IL-1 $\beta$ -induced inflammation, reactive oxygen species production, cell cycle activation, and apoptosis in chondrocytes. The author concluded that SB could attenuate OA progression by restring impaired autophagy and autophagy-flux via the phosphoinositide 3-kinase/ protein kinase B/mammalian target of rapamycin pathway, both in vitro and in vivo, implying that SB could represent a novel therapeutic approach for OA.

## THE EFFECTS OF HYALURONAN DURING THE DEVELOPMENT OF OSTEOARTHRITIS AND THE SKIN HEALTH

Several meta-analyses of hyaluronan (HA) for knee osteoarthritis have been conducted with conflicting results: Compared with low-molecular weight HA, the highest-molecular HA may be more efficacious in treating knee osteoarthritis (OA), but heterogeneity of these studies limits definitive conclusions<sup>[30]</sup>. A meta-analysis of randomized controlled trials on therapeutic effects of HA on knee osteoarthritis by intra-articular injection of HA was demonstrated by Richette *et al*<sup>[29]</sup>.

The meta-analysis confirmed the therapeutic efficacy and safety of intra-articular injection of HA<sup>[31]</sup>. Intra-articular injection of HA can decrease symptoms of knee OA. Wang *et al*<sup>[31]</sup> found significant improvements in pain and fundamental outcomes with few adverse events. Neustadt *et al*<sup>[32]</sup> evaluated the efficacy and safety of injection of high molecular weight (HMW) HA (Orthovisc) in knee OA, using a randomized, controlled and multicenter trial. The author indicated that HMW-HA is safe and seems to be effective in the treatment of mild to severe knee OA.

Tashiro *et al*<sup>[33]</sup> investigated the efficacy of oral hyaluronic acid (HA, molecular weight: 900,000: on HPLC, a single peak of 97% purity) for OA in knee joint. Sixty osteoarthritic subjects (Kellgren-Lawrence grade 2 or 3) were randomly assigned to the HA or placebo group. The subjects in the HA group were given 200mg of HA once a day every for 12 months, while the subjects in the placebo group were given placebo. The improvement of the subjects as determined by JKOM score improved with time in both the HA and placebo groups. This improvement tended to be more obvious with the HA group, and this trend was more obvious with the subjects aged 70 years or less.

Hsu *et al*<sup>[34]</sup> conducted a placebo-controlled, randomized, double-blind trial of daily HA (120mg) intake for 12 weeks in 40 healthy Asian men and women (aged 35-64 years). Skin condition was

determined by the evaluation of wrinkles, stratum corneum water content, the amount trans-epidermal water loss, elasticity, and through image analysis. The author found that oral ingestion of HA may suppress wrinkles and improve skin condition.

## EXTRACTION OF HA FROM ALOE VERA JUST BELOW THE WAXY CUTICLE OF RIND

Putri *et al.*<sup>[35]</sup> found HA on *Aloe vera* just below the waxy cuticle of rind, these in an area where aloe correlated bacteria live. Gram-positive microbes *Streptococci* which are able to produce HA through bacterial pathway were only found on the surface of *Aloe vera*, whereas *Coccobacilli* are observed only in gel part. The rind part of *Aloe vera* had the highest potential of high content of HA.

## EFFECTS OF ORAL HYALURONIC ACID ADMINISTRATION IN RATS, DOGS AND PATIENTS

On the absorption of HA, Oe *et al.*<sup>[36]</sup> confirmed the absorption, migration, and excretion of <sup>14</sup>C-hyaluronic acid was orally or intravenously administered to male SD rats aged 7 to 8 weeks. Aguado *et al.*<sup>[37]</sup> evaluated the effects of oral HA administration on synovial fluid concentrations of several selected biomarkers in dogs with cranial cruciate ligament (CCL) injury operated on using the tibia tuberosity advancement technique. The post-op oral HA administration in canine patients with CCL injury led to improvements in osteoarthritis biomarkers, namely higher synovial fluid HA concentrations and the reduced synovial fluid paraoxonase-1 concentrations. Furthermore, Hsu group's report<sup>[34]</sup> demonstrated that oral ingestion of HA for 12 weeks may improve wrinkle control and skin condition in healthy Asian men and women aged 35-64 years. Thus, the daily consumption of HA may be used as a functional food that contribute to the development of osteoarthritis and the maintenance of skin health.

## THE SHORT-TERM ORAL SODIUM HYALURONIC ACID FORMULATION ON KNEE OSTEOARTHRITIS: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Sodium hyaluronic acid with a large spectrum of molecular weight (FS-HA) on symptoms and functionality of knee osteoarthritis (OA) was tested in pilot study by Cicero *et al.*<sup>[38]</sup>. Sixty 30-85 years old male and female with BMI < 35 kg/cm<sup>2</sup>, affected by clinical and/or radiological diagnosis of symptomatic knee OA were consecutively enrolled in a randomized, double blind, placebo-controlled and clinical trial. The oral supplementation of a FS-HA, patented HA characterized by a large spectrum of molecular weight, with daily 200mg ingestion for 8 weeks, was associated with a short-term improvement in symptomatology and functionality of osteoarthritis-affected knees, and associated with a reduction in the use of non-steroidal anti-inflammatory drugs and anti-pain drugs.

The findings supported the bioavailability of orally-administered HA and its usefulness in improving biomarkers of osteoarthritis.

## CASE REPORTS

**Case report 1:** Beneficial role of *Aloe vera* juice (AVJ) to migraine

and movement<sup>[6]</sup>.

A female had been migraine nauseous, dizzy and ear noise since 18-years old. Doctor administered several medical treatments but she did not recover. She had two children after she become a nurse.

When she was 40-years-old, she had a traffic accident on Oct. 2019. Then, her past medical history was clarified to be Chiari malformation syringomyelia. The doctor administered drugs and recommended a large exhalent decompression, but she denied take drugs and surgery. She started to ingestion of AVJ 1500ml/day since Dec. 2019. Now she is no migraine and nauseous, and has a well movement with well QOL.

**Case report 2:** Recovery of dermatologic microscopic polyangiitis: Prednisolone withdrawal with kampo medicine, Rokumigan, and *Aloe vera* juice (AVJ)<sup>[9]</sup>.

A ~50-years-old female being hard and strong fatigues after job change, had heavy pain and swollen around both ankles on 2010, and coloration of the ankles changed to purple. Skin biopsy did not show exact illness. She retired from the job on 2015 and was hospitalized and diagnosed to be dermatologic microscopic polyangiitis (DMP). She took prednisolone (5mg/day) and azathiopurine (50mg/day) for 50 days from May, 2018. And she started to ingest AVJ, 660ml/day with prednisolone (4mg/day) on July, 2020, and then AVJ (1000ml/day) with Kampo medicine (Rokumigan) on Oct, 2020. Finally, she only ingested AVJ (660ml/day). Since then, she recovered for DMP and had well QOL.

## SUMMARY

Association of aloe vera gel extract and butyrate fermented with bone-muscle generation, such as osteoarthritis and rheumatoid inflammation, was discussed on the base of the biomedical management. The short-term effect of oral sodium hyaluronic acid with a large spectrum of molecular weight on the symptoms and functionality of knee osteoarthritis was evaluated. And case report 1 showed that supplementation of AVJ may be suggested the enhancement of connective tissue recovery via angiogenesis. In case report 2, the recovery of dermatologic microscopic polyangiitis and the prednisolone withdrawal with Kampo medicine, Rokumigan and AVJ were exhibited.

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