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Possible Epigenetic Role of Butyrate Fermented in Aloe Vera Gel on Kidney Function and Chronic Hepatitis: Case Reports

A Yagi[1]*, M Hasegawa[2] and K Shiba[3]

[1]*Special Adviser of Japan Aloe Science Association, Professor Emeritus of Fukuyama University, Hiroshima, Japan*

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

[3]*A Clinic Director in Yokohama City, Kanagawa, Japan*

***Corresponding Author:** A Yagi, Special Adviser of Japan Aloe Science Association; Professor Emeritus of Fukuyama University, Hiroshima, Japan.

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Abstract

The successive ingestion of aloe vera juice (AVJ) provided high concentration of butyrogenic microbiome, *Faecalibacterium* spp. and *Clostridium* spp. in fecal. Intestinal flora changes of chronic kidney disease and end-stage renal disease patients were discussed and the participation of butyrate fermented in aloe vera gel was reviewed. The mechanism and pathways with histone deacetylase inhibitor, butyrate in nephrotic syndrome in the patients with kidney disease and the gut butyrogenic microbiome alteration in hepatitis C patients were described. In case report 1 we showed an adjuvant-like activity of successive ingestion of AVJ with Kampo medicine to nephrosis and in case report 2 we exhibited the successive activity of AVJ ingestion after operation of hepatic carcinoma.

Keywords: *Aloe Vera Juice (AVJ); Butyrate; Kidney Function; Chronic Hepatitis*

Introduction

Long-term ingestion of water soluble aloe vera gel juice influences the microbial activity in human gut. The prebiotic activity of aloe vera juice (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 and could play a beneficial role for tissue repair and bone regeneration [2]. Abdal., *et al*. [3] examined the role of aloe vera gel extract on lipid characters, liver and kidney functions in rats and estimated that aloe vera gel extract is effective to increase the lipid character, liver and kidney functional changes induced by hydrogen peroxide in rats. Alternations in serum electrolytes, urea, and creatinine in aloe vera gel-treated rats were examined by Saka., *et al* [4]. The authors obtained that aloe vera gel extract damages renal directing of electrolytes with resulting in hyponatremia and hypercreatinemia.

In the previous papers we described the effect of fermented butyrate in aloe vera gel and barbaloin to chronic kidney disease and uremic toxins; indole sulfate and p-cresol [5] and beneficial roles of AVJ to children with steroid-sensitive nephrotic syndrome (minimal change nephrotic syndrome with edema around eyes) [6].

In present review we describe the mechanism and pathways associated with histone deacetylase inhibitors, butyrate, in nephrotic syndrome, and case reports; the adjuvant-like effect of aloe vera juice (AVJ) for nephrosis with Kampo medicine and the successive ingestion of AVJ after surgery of hepatic carcinoma.

The physiological efficacy and effect of all-trans-retinoic acid and sodium butyrate in improving the renal fibrosis and inflammation in Npr 1 gene-splitting haplotype male mice

Kumar P (Pandey KN group)., *et al*. [7] searched to draw the mechanisms of guanylyl cyclase/atrial natriuretic peptide receptor (GC-A/NPRA) gene (*Npr1*) expression *in vivo*, by use of all-trans retinoic acid (ATRA) and histone deacetylase inhibitor (HDACi), sodium butyrate (NaBu) to test the expressions and characteristic actions of *Npr1* by use of gene-disrupted heterozygous, wild-type, and gene-duplicated heterozygous mice. The authors found that epigenetic upregulation of *Npr1* gene transcription by ATRA and NaBu orders to weaken renal fibrotic markers and systolic blood pressure in mice with reduced number of *Npr1* gene copy. They will have significant suggestible ideas in prevention and treatment of hypertension-related renal pathophysiological conditions. The current finding by the authors will help in development of the molecular therapeutic targets and new tactics for hypertension and renal dysfunction in human [8].

Sodium butyrate; a known activator of nuclear factor erythroid 2-related factor 2, will help diabetic nephropathy via inhibition of HDAC

Better understanding of the butyrate action mechanism in intestinal physiology and lipid metabolism will advance to apply butyrate (HDAC inhibitor) in gut health control, and to prevent metabolite diseases such as obesity, insulin resistance and diabetes, as the efficacy of gut microbiome are various on health maintenance. Daily ingestion of AVJ that increases butyrate levels may effectively support to establish mild state of T2D diabetes and obesity [9]. The prolonging effect of a life-long ingestion of aloe vera prohibited the happening and strictness due to the age-related diseases by weakening the age-associated physiological decline in male Fisher 344 rats [10].

Sodium butyrate ameliorates diabetic nephropathy via inhibition of histone deacetylase inhibition activity

Oxidative stress gives the pathogenesis of diabetic nephropathy (DN). Nuclear factor erythroid 2-related factor 2 (Nrf2) performs a leading role in the cellular-defensive system against oxidative stress. Nrf2 activators have led to successfully preventive effects on DN. Dong., *et al*. [11] investigated whether Nrf2 is required for sodium butyrate (NaB) protection against DN. The streptozotocin-induced diabetic C57BL/6 Nrf2 knockout and their wild-type mice were managed with the presence or absence of NaB during 20 weeks. The deletion of the Nrf2 gene completely abolished NaB activation of Nrf2 signaling and fully defended against diabetes-induced renal injury. Nrf2 nuclear translocation was not advanced by treatment of NaB. Therefore, the authors showed that Nrf2 acts a controlling position in NaB protection against DN, and suggested that NaB may activate Nrf2 at the transcriptional level by the possible HDAC inhibition. Khan and Jena [12] investigated the reno-productive efficacy of NaB in diabetes-induced renal damages such as apoptosis and fibrosis in juvenile rats. Diabetes was induced by single injection of streptozotocin, whereas NaB was administrated by intraperitoneal route in a pre- and post-treatment schedule during 21 days. The results indicated that NaB administration made better the renal function and amended the histological changes, fibrosis, apoptosis and DNA damages in the kidney of juvenile rats.

The gut microbial main outline in adults with kidney disease and kidney stones and current therapies in nephrotic syndrome

There is a lot of supporting evidence that individuals with kidney disease and kidney stones have an abnormal gut microbiome composition. Stanford., *et al*. [13] examined the gut microbial community in adults gut with kidney disease or kidney stones by comparing this to the controls. Six scientific databases were searched and distinguishing deviation in the functional potentiality of the microbial community between controls and adults with kidney disease or kidney stones were identified. Nephrotic syndrome (NS) is one of the chief chronic kidney conditions happening in children and adults with distinguishing characteristics of podocyte injury. Presently, therapy for NS contains a variety of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, monoclonal antibodies, steroids, and immune-suppressants. Steroidal drugs are the initial treatment for NS patients and are thought of the fundamentally first approach for the therapy. Recently histone deacetylase inhibitors (HDACi) have been greatly searched into the treatment of chronic kidney diseases.

They revealed anti-fibrotic, anti-inflammatory, and immunosuppressive effect. Varghese., *et al*. [14] reviewed that targeting HDACs can be a favorable therapeutic strategy to treat NS, and outlined the potential use of HDACi as an alternative therapy in treatment of NS.

Dysbiosis of gut microbiota in adult and child with idiopathic nephrotic syndrome

Zhang., *et al*. [15] reported the gut microbial changes in idiopathic nephrotic syndrome (INS) patients with a membrane-like nephropathy. The gut microbiome composition was analyzed by use of a 168 ribosomal RNA gene-based sequencing protocol. The author exhibited the apparent alterations in the gut microbiome of CKD and INS. Short chain fatty acid-producing bacteria were decreased, thereby short chain fatty acids, such as butyrate, decreased in INS patients.

Idiopathic nephrotic syndrome in children: Clinical significance of probiotics and the role of regulatory T cells

Tsuji., *et al.* [16] reported that a decrease in butyrate producing bacteria in the gut is a possibly active cause due to irregular T cells (Tregs) in children with idiopathic nephrotic syndrome (INS). Tregs were measured by flow cytometry, and gut microbiota composition was assessed using 16S ribosomal RNA sequencing. A low rate increase in Tregs is connected with the following frequent relapses of INS. And the increase in Tregs in response to steroidal drug treatment was small when dysbiosis was introduced into patients with INS, particularly when the proportion of butyrate-producing bacteria was considerably reduced. The authors [17] furthermore investigated the administration of butyrate-producing bacteria for reducing INS relapse and the need for immune-suppressants in these 20 patients in remission from INS (median age 5.3 years, 15 boys). In the probiotic treatment with a preparation of 3g *Clostridium butyricum* group, the analyses before and after probiotic treatment revealed the significant increases in the relative abundance of butyrate-producing bacteria and blood Treg counts. Thus, the oral application of butyrate-producing microbiota during INS remission may diminish the frequency of relapse and the need for immunosuppressive agents.

Alteration of intestinal flora producing butyrate in patients with end-stage renal disease and chronic kidney disease

Chronic kidney disease (CKD) is connected with the diminishing intestinal barrier function, which caused bacterial translocation over the intestinal wall and triggered a systemic inflammatory response.

Jian., *et al*. [18] estimated differences in the compositions of fecal microbiota between 52 end-stage renal diseases (ESRD) patients and 60 healthy controls in southern China by use of quantitative real-time polymerase chain reaction (qPCR) and high-throughput-sequencing methods. The butyrate producing microbiome, *Roseburia, Faecalibacterium, Clostridium, Coprococcus* and *Prevotella* were diminished in the ESRD group. In qPCR analysis, the butyrate producing species: *Roseburia* spp, *F. prausnitzii, Prevotella* and Universal bacteria, were negatively related to C-reactive protein and Cystatin C. Thus, the gut microbiota has a good connection with the inflammatory state and renal function of CKD.

Terpstra., *et al*. [19] examined that (i) if Dutch patients with end-stage renal disease (ESRD) have a diminishing amount of butyrate-producing microbial species and butyrate-producing capability, and (ii) whether this is correlative to the systemic inflammation. The authors did not find a significant difference in the amount of the most abundant butyrate producing microbial species or in the butyrate producing capability between ESRD and healthy kidney donors. Neither was there a significant correlation with C-reactive protein (CRP), Il-6 (markers of inflammation) or D-lactate (reflecting the intestinal barrier function). Among the dialysis patients, the variability was high and the authors did identify patients with low amounts of the butyrate-producing species (*Faecalibacterium, Eubacterium, Roseburia* spp.), a low butyrogenic capacity and high inflammatory markers (CRP, IL-6) or intestinal permeability (D-lactate). Liu., *et al*. [20] prepared the intestinal floral changes of CKD patients engaged in different hemodialysis therapy. Patients were recruited during 2017 - 2019 and sectionalized into healthy control group (CT), CKD non-dialysis group (CKD), hemodialysis group (HD), and peritoneal dialysis

(PD) group. 16S rRNA sequencing analysis of intestinal flora genome and further bio-informatics analysis were performed. The results suggested that peritoneal dialysis (PD) therapy could result in diminished diversity and innovated microbial communities, containing reduced probiotic butyrate-producing taxa and increased urease containing, indole- and p-cresol-forming taxa.

The confused intestinal flora can seriously affect the nutrition level in CKD patients with PD therapy. Frailty is prevalent in older patients affected by CKD. Since gut microbiota (gMB) may contribute to frailty, Margiotta., *et al*. [21] explored credible association between gMB and frailty in CKD. The authors investigated 64 CKD patients (stage 3b-4), categorized as frail (F, 38) and not frail (NF, 26) according to Fried criteria, and 15 control (C), all older than 65 years. No difference in α diversity between CKD and C and between F and NF patients emerged, but high-throughput sequencing showed significantly higher abundance of potentially noxious bacteria (*Citrobacter, Coprobaccillus*) and lower abundance of saccharolytic and butyrate-producing bacteria (*Prevotella* spp, *Faecalibactrium prausnitzii, Roseburia* spp.), in CKD respect to C. The results suggested that inflammation and frailty could be deeply associated to gMB modification in CKD.

Intestinal flora changes of chronic kidney disease patients undertook different hemodialysis therapy

High-throughput sequencing analysis of intestinal flora changes in CKD and end-stage renal disease patients recruited during 2017 - 2019, was performed by Hu., *et al* [22]. The patients were divided into health control group (CT), CKD non-dialysis group (CKD), hemodialysis group (HD) and peritoneal dialysis group (PD). Intestinal flora genome 16S rDNA sequencing and further bioinformatics analysis were performed. The authors suggested that peritoneal dialysis therapy could result in reduced diversity and altered microbial communities, with reduced probiotic butyrate-producing taxa (*Faecalibacterium* in genera level and *Bifidobacteriaceae* and *Prevotellaceae* in family level) and increased urease containing, indole and p-cresol forming taxa (Escherichia in genera and *Enterobacteriaceae* and *Enterococcaceae* in family level). The disordered intestinal flora can seriously affect the nutrition level in CKD patients with PD therapy.

Quantitative reduction in SCFAs, especially butyrate contributing to the progression of CKD

Wang., *et al*. [23] evaluated the levels of SCFAs in healthy and CKD patients, and to test the hypothesis that SCFAs plays a critical role in delaying CKD progression. One hundred and twenty-seven patients with CKD and 63 healthy controls from China were enrolled in the present study. Butyrate was almost three-times higher in healthy volunteers than that in CKD5 subjects ($p < 0.001$). Moreover, the serum SCFAs levels in controls were significantly higher than that in CKD patients ($P < 0.05$), and the butyrate level among CKD5 patients (1.48 ± 0.60 μmol/L) was less than half of that in controls (3.44 ± 2.12 μmol/L, $p < 0.001$). The results showed that SCFA levels were reduced in CKD patients and that butyrate supplementation might delay CKD progression.

Quantitative reduction of gut microbiota-derived SCFAs in diabetic kidney disease

A total of 30 participants with type 2 diabetes mellitus-dietary kidney disease (DKD) and 30 normal controls in HwaMei Hospital were recruited by Zhong., *et al*. [24] from 1/1/2018 to 12/31/2019. The study provided evidence that in individuals with DKD, serum and fecal SCFAs levels (fecal level in particular) were lowered. There was a correlation between lower SCFAs (acetate, propionate and butyrate) and a worsened renal function, demonstrating the association of SCFAs with worse renal functions in DKD.

MicroRNA expression profiling in diabetic kidney disease

The microRNAs (miRs) that can regulate diabetic kidney disease (DKD) have not fully characterized. Ishii., *et al*. [25] investigated the miRs that can regulate diabetic DKD and identified the miRs that affect DKD and could be used as specific biomarkers or therapeutic agents. Among them miR-125b-5p and miR-181b-5p were exclusively downregulated in the DKD mouse model. The serum level of miR-125b-5p was significantly higher in patients with DKD (1.89 ± 0.40-fold, $p < 0.05$) compared with patients with other kidney disease (0.94 ± 0.13-fold) and healthy subjects (1.00 ± 0.19-fold). Serum levels of miR-181b-5p were lower in patients with DKD compared with

patients with other kidney diseases and healthy subjects. These results suggest that miR 181b-5p and miR125b-5p may represent novel diagnostic biomarkers and that miR 181b-5p may represent a therapeutic target for DKD.

MicroRNA-451 as an early predictor of CKD in diabetic nephropathy

Diabetes mellitus is the leading cause of end-stage renal disease worldwide. MicRs are not only new and promising markers for early diagnosis but they may play a role in the prevention of disease progression. Abdelsalam., *et al*. [26] investigated that MicR-451 expression in blood and plasma using real-time PCR was elevated in addition to the classic diabetic nephropathy markers (serum creatinine, urinary albumin, and estimated glomerular filtration rate (eGFR). eGFR showed a positive correlation with urinary micR-451 and negative correlation with both plasma micR-451 and urinary albumin. Both plasma and urinary micR-451 are highly sensitive and specific markers for chronicity in diabetic nephrosis. MicR-451 is a promising early biomarker for chronic kidney disease in diabetic nephropathy with high sensitivity and specificity.

Butyrate protects against proteinuric kidney disease through epigenetic-and GPR109-mediated mechanisms

Butyrate inhibits histone deacetylases, thereby affecting gene transcription, and also signals through the metabolite-sensing G protein receptor (GPR) 109a. Felizardo., *et al*. [27] produced an monoclonal antibody (mAb) to mouse GPR109a and found high expression on podocytes in the kidney. Wild-type and GPR109a$^{-/-}$ mice were induced to develop nephropathy by a single injection of adriamycin and treated with sodium butyrate or high butyrate-releasing high-amylose maize starch diet. Butyrate improved proteinuria by preserving podocyte at glomerular basement membrane and attenuated glomerulosclerosis and tissue inflammation. The authors found that GPR109a is expressed by podocyte, and the use of GPR109a$^{-/-}$ mice showed that the protective effects of butyrate depended on GPR109a expression. A prebiotic diet that releases high amounts of butyrate also proved highly effective for protection against kidney disease. Butyrate and GPR109a play a role in the pathogenesis of kidney disease and provide one of the important molecular connections between diet, the gut microbiota, and kidney disease.

Effect of Aloe vera gel on relief of hemodialysis patient's pruritus and in providing xerosis repair in chronic kidney failure patients

Pruritus is one of the most common problems in patients with kidney failure. Malekhoseini., *et al*. [28] evaluate the effect of Aloe vera gel on pruritus in hemodialysis patients. The clinical trial was conducted on 60 hemodialysis patients with moderate and severe uremic pruritus in the hospitals affiliated to Arak University of Medical Sciences. The mean pruritus before and after the intervention in the group two groups of 30, treated by Aloe vera gel was 5.53 ± 1.73 and 2.03 ± 1.12, respectively ($p = 0.001$). In the control group, it was 5.96 ± 1.03 and 5.90 ± 0.75 ($p = 0.423$). Since many drugs used to treat pruritus in dialysis patients are expensive and cause problems such as allergies and drug resistance, it is recommended that these patients use of Aloe vera gel to control their itchy skin condition. Handriani., *et al*. [29] used simple random sampling technique to recruit 25 responders. Aloe vera extract was used by rubbing it onto the skin with xerosis and assessment was conducted in the first, second and third week. The result of different test was $p = 0.001$, showed that there was significant differences between groups of independent variables. Aloe vera extract had an effect as much as 69% of improvement in skin conditions of xerosis patients and 31% was influenced by other factors besides Aloe vera extract. Aloe vera could be a therapy for xerosis as a management of independent nursing care with nursing problems of skin integrity disorders.

Gut-liver axis in liver viral hepatitis

The liver is directly connected to the intestinal tract by the portal vein, and the intestinal factors play a very important role in the onset and progression of liver diseases through enterohepatic circulation.

Aloe vera is one of the most popular plants and has been used frequently for alternative drugs for the treatment of liver diseases. Bhatt., *et al*. [30] enrolled that a total of 110 male and female patients, aged between 15 - 65 years, diagnosed clinically and biochemically as the case of acute viral hepatitis. Subjects were randomized into two groups. Fifty patients belonging to control group received conventional treatment for acute viral hepatitis, while 60 patients enrolled in treated group were given conventional treatment for acute viral hepatitis supplemented with aloe vera juice in dose of 20 ml orally for 6 weeks. Serum bilirubin, ALT, AST and ALP levels were measured initially and at the end of 2, 4 and 6 weeks. Intragroup comparison decreased statistically and significantly in the parameters for both treated and controlled groups at all intervals of time. Intergroup comparison revealed statistically significant differences in all the mentioned parameters between treated and controlled groups at all intervals of time.

Antifibrotic effect of aloe vera high molecular weight molecule (AHM) in viral infection-induced hepatic periportal fibrosis

Aloe vera gel has been demonstrated to have liver protective effects in rats, and many toxicity studies have been conducted to determine the LD50 of aloe vera. Hepatic fine periportal fibrosis is a common response to liver injury caused by fibrosis provoked by excessive hepatocytes apoptosis and necrosis. Our previous study investigated the anti-fibrotic effects of AHM for patients with acute liver fibrosis [31]. Among the 40 patients 15 patients had HCV, 24 and had HBV and 1 had bilharziasis. All the patients were diagnosed according to the International Autoimmune Hepatitis Group Report protocol. The patients were randomly subdivided into two equal groups: the conventional group treated with the conventional treatment with placebo (starch) for 12 consecutive weeks, and the AMH group treated with the conventional treatment with 0.15 g/d AHM (0.05g three times daily) for 12 consecutive weeks. The serum ALT, AST and ALP activities were significantly higher in the patients at the beginning of the study as compared with the control group. These increases were attenuated after treatment in both the conventional group and the AHM group, and the decreases in the AHM group were more significant than in the conventional group. There was no significant difference in the liver enzyme activities between HBV-induced fibrosis and HCV after treatment. The AHM preparation has anti-fibrotic effects which could be attributed to its ability to attenuate oxidative stress, and enhance the collagenolytic activity and provided evidences that AMH could be used as an adjunct treatment to prevent or treat hepatocellular damage in hepatic fine periportal fibrosis.

The role of intestinal microbiota in chronic hepatitis C infection

In a cross-sectional approach, Heidrich., *et al*. [32] analyzed the intestinal microbiota of 95 patients chronically infected with HCV (n = 57 without cirrhosis; n = 38 with cirrhosis) and 50 healthy controls without documented liver diseases. The study showed that not only the stage of liver disease but also HCV infection is associated with a reduced alpha diversity measured by number of phylotypes and Shannon diversity index, and different microbial community patterns. These differences might be caused by direct interactions between HCV and the microbiota or indirect interactions facilitated by the immune system.

Role of gut microbiota in hepatitis B and C infection

Dysbiosis of gut microbiota in chronic hepatitis B infection affects disease pathogenesis and causes liver failure in a large population. Liu., *et al*. [33] investigated 16S rRNA analysis in a cohort of 33 healthy controls, 35 individuals with HBV related hepatocellular carcinoma (B-HCC) and 22 individuals with non-HBV non-HCV (NBNC) related HCC (NBNC-HCC). The feces of NBNC-HCC patients harbored more potential pro-inflammatory bacteria (*Escherichia-Shigella, Enterococcus*) and reduced levels of *Faecalibacterium, Ruminococcus*, *Ruminoclostridium* which results in decrease potential of anti-inflammatory short chain fatty acids, butyric acid. The modification of specific gut microbiota may provide the therapeutic benefit for B-HCC and NBNC-HCC.

Hepatis C virus (HCV) causes debilitating liver diseases, which may progress to cirrhosis and cancer. Aly., *et al*. [34] studied to monitor differences in the gut microbial community composition of Egyptian HCV patients that may affect or result from the patients' liver state. Whereas members of phylum *Bacteroidetes* were more abundant in HVC patients, healthy individuals had higher abundance of *Firmicutes,*

Proteobacteria and *Actinobacteria*. Genus-level analysis showed differential abundance of *Prevotella* and *Faecalibacterium* (higher in HCV patient) vs. *Ruminococcus* and *Clostridium* (healthy group), indicating that the higher abundance of Bacteroidetes in HCV patients is most likely due to *Prevotella* overabundance. The probiotic genus, *Bifidobacteium*, was only observed in the microbiota of healthy individuals.

The relationship between butyrate supplementation and dysregulated bile acid synthesis-induced hepatitis

Dysregulated bile acid (BA) synthesis is found in patients having metabolic diseases, autoimmune hepatitis, and liver cirrhosis or cancer. Sheng., *et al*. [35] investigated the relationship between butyrate and dysregulated BA synthesis-induced hepatitis as well as the effect of butyrate in reversing the liver pathology. The authors concluded that reduced butyrate supplementation in wild-type and farnesoid X receptor (FXR) knockout (KO) male mice, placed on a control or western diet for 15 months, contributes to the development of hepatitis in the FXR KO mouse. Thus, butyrate reverses dysregulated BA synthesis and its associated hepatitis.

Microbiota-gut-liver axis in HCV infection

HCV infection induces physiological changes in both the liver and the intestine, such as bile acid disturbance, which in turn, affects the microbiota diversity and structure. Chronic HCV infections are associated with enrichment of potentially harmful bacteria such as *Enterobacteriacea* and depletion of potentially beneficial microbes such as *Ruminococcaceae* and *Lachnospiraceae*. These changes are related to the progression of the diseases and to the studied cohort. El-Mowafy., *et al*. [36] discussed that HCV is associated with gut microbiota dysbiosis and distortion of bile acid metabolism, which overtime promote liver complications and cross talk with HCV treatment regimens.

Case reports 1: Treatment of a nephrosis patient with Kampo; Rokumigan with aloe vera juice

A 60-years-old female who had horrible swelling feet, showed occult blood +, protein +4 on a blood test. She diagnosed with nephrosis on February, 2017. She was administrated prednisolone 25 mg/day and cyclosporine 10 mg/kg/day. She still had swelling feet and showed occult blood 2+, protein urea 3+, blood albumin 2.7 g/dL and LDL cholesterol over 206/dL on a blood test on March, 2018. Then she continued to take prednisolone 25 mg/day and cyclosporine 5 mg/kg/day and the blood test showed occult blood ±, protein urea 3+, LDL cholesterol 276/dL, blood sugar level 127 mg/dL, albumin 3.6 h/dL, creatinine 1.04 mg/dL, uric acid 7.5 mg/L, and Hb-Alc 7.5%. After drugs administration her blood test was clear but diastolic blood pressure showed 200 mmHg and body weight changed from 49 kg to 68 kg on July, 2019. Then she decided to drug deprivation and administered Kampo: Rokumigan with aloe vera juice (AVJ) 330 ml/day and half amount of prednisolone without cyclosporine. On February, 2020 her body weight changed from 68 kg to 51 kg and diastolic blood pressure 180 mm/Hg, protein urea -, occult blood pressure -, albumin 4.3/dL, creatinine 0.7 mg/dL and diagnosed no edema. Finally, she deprived prednisolone and continue to take AVJ 330 ml/day and nephrosis based on the blood test showed normal level. The doctor diagnosed remission of nephrosis on July, 2021.

Case report 2: Treatment of a hepatic carcinoma patient in hospital

A 56-years-old female who had hyperthyroidism in her clinical history, showing GOT 182 and GPT 236 on blood examination, diagnosed hepatitis C and hospitalized interferon injection for one month in the hospital on May, 1995. She started to ingest AVJ 30 ml/day on December, 1996 and had normal blood examination level on August, 1998. When she had liver function test by second-opinion-doctor, hepatocellular carcinoma was identified and the tumor removal-surgery was carried out on May, 2009. The metastases in her left inguinal region were identified and hospitalized for X-ray treatment on September, 2010. Based on the examination of bone scintigraphy, multiple vertebral metastasis were recognized, and she administrated nexavar (sorafenib tosilate) tablet 200 mg on October, 2011. After the discharge the hospital, she had body flare. She diagnosed drug rash by dermatologist. Since then, she successively ingested AVJ 300 ml/day without the drug. She had herpes zoster on March 2012 and recovered with AVJ, pollen, and propolis. She had a recurrence of hepatic carcinoma on March, 2015 and performed re-operation of surgery. She started to successive ingestion of AVJ 400ml/day with pollen and

propolis. On May, 2015 she safely discharged. She had chronic hepatitis C recurrence on February, 2016, and diagnosed Harvoni (combination of ledipasvir and sofosbuvir) 1 tablet/day for 12 weeks, and the doctor diagnosed remission of chronic hepatitis. On September, 2019 she had colonoscopy and three colorectal polyps were removed. Since then, she had been well-QOL with successive AVJ ingestion to June, 2020.

Discussion in Case Reports

Long-term ingestion of AVJ after the deprivation of steroid and anti-inflammatory drugs provided well-being QOL. The successive ingestion of AVJ provides high concentration of the butyrogenic microbiome *Faecalibacterium* spp. and *Clostridium* spp. in fecal [2] and could play a beneficial role for kidney. As shown in previous paper we reported the risk-remissions for steroid-induced osteonecrosis of femoral head after nephrotic kidney syndrome and steroid treatment to minimal change nephrotic syndrome by use of Kampo medicine; Rokumigan with AVJ [6]. These treatments may support the remission of nephrotic syndrome. Successive ingestion of AVJ as an adjuvant-like action in present case report 1 may be effective for protection against kidney disease by providing butyrate function. A 56-years-old female who had hyperthyroidism in her clinical history and hepatitis C, had been fighting against hepatitis during about 20 years. On July, 2020 at 81-years-old she had been well QOL with successive ingestion of AVL supplement in case reports 2.

Summary

In our previous report [6] the risk-remission for steroid-induced osteonecrosis of femoral head after nephrotic kidney syndrome in child with successive ingestion of aloe vera juice and the risk-remission for steroid treatment to minimal change nephrotic syndrome were exhibited. A prebiotic diet or a successive ingestion of aloe vera juice (AVJ) that releases high amount of butyrate provided highly effective for protective against kidney disease. In case report 1 AVJ as an adjuvant-like action with Kampo: Rokumigan was demonstrated. A frail female having hepatitis C in case report 2, had several medical treatments and liver surgery, and she had been well QOL after a successive ingestion of AVJ supplement which may support and recover liver homeostasis.

Aloe vera gel extract is effective to improve the liver and kidney functions and the discoveries of novel low-cost herbal drug of natural non-toxic origin are promising for developing countries.

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