

Beneficial Roles of Aloe Fermented Butyrate, Propionate, and Aloin to Chronic Kidney Disease and Uremic Toxins

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

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Received: October 20, 2019

Revised: October 25, 2019

Accepted: October 26, 2019

Published online: December 21, 2019

ABSTRACT

In this review, we exhibit the efficacy of endophytically fermented aloe butyric and propionic acid to improve kidney function. Furthermore, renal protective effect of aloe plant extract and aloin is discussed to chronic kidney disease and uremic toxins.

Key words: Butyrate; Propionate; Endophytically fermented aloe plants extract; Aloin; Chronic kidney diseases; Uremic toxins

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Koizumi K, Hasegawa M, Mukaitani A, Yagi A. Beneficial Roles of Aloe Fermented Butyrate, Propionate, and Aloin to Chronic Kidney Disease and Uremic Toxins. *Journal of Gastroenterology and Hepatology Research* 2019; **8(6)**: 2997-3002 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2755>

INTRODUCTION

Findings from Human Microbiome Projects on 2009 and the Metagenomics of the Human Intestinal Tract Project on 2010 have shown that the human intestine is home to an extraordinarily complex and dynamic consortium of bacteria that play a pivotal role in human health and disease. The gut microbiome plays important roles in both the maintenance of health and the pathogenesis of disease. The symbiotic relationship between host and microbiome is disturbed due to the proliferation of dysbiotic bacteria in patients with chronic kidney disease (CKD). Fermentation of protein and amino acids by gut bacteria generates excess amounts of potentially toxic compounds such as ammonia, amines, thiols, phenols, and indoles, but the generation of short chain fatty acids is reduced.

Reducing the accumulation of uremic toxins through modification of gut microbiota is, therefore, important for the protection against for renal damage.

An altered dysbiotic gut microbiome will not only produce an array of harmful metabolites and uremic toxins, but also potentially cease to produce the otherwise beneficial metabolites such as short chain fatty acid (SCFA). The SCFA enter the systemic circulation through colonocytes by passive diffusion as well as active transport mechanisms. Butyrate is the primary source of energy for colonocytes and is thus associated with maintenance of epithelium. Ramezani *et al*^[1] showed the role of SCFA to explain the gut-kidney connection in ischemia reperfusion injury showing that treatment with SCFA reduces kidney injury of this type in a germ-free mouse model system. Mishima *et al*^[2] compared adenine-induced renal failure and control mice under germ-free or specific pathogen-free (SPF) conditions, examining the metabolite profiles of plasma, feces, and urine using a capillary electrophoresis time-of-flight mass spectrometry-based approach. Germ-free renal failure conditions resulted in the disappearance of colonic short-chain fatty acids (butyric, propionic and succinic acid), decreased utilization of intestinal amino acids, and more severe renal damage compared with

SPF mice with renal failure. Microbiota-derived SCFAs and efficient amino acid utilization may have a renoprotective effect, and loss of these factors may exacerbate renal damage in germ-free mice with renal failure.

Gut microbiota is involved in the metabolism of uremic solutes in CKD. A leaky gut happens when food allergens or bacterial infections cause the intestinal wall to no longer do its job in regulating the passage of substances from entering or leaving the body. A leaky gut contributes to CKD progression and CKD complications. Anders *et al*^[3] discussed how the metabolic alterations of uremic favor pathogen overgrowth (dysbiosis) in the gut and an increased translocation of living bacteria and bacterial components. This process has the potential to activate innate immunity and systemic inflammation. Wong *et al*^[4] found marked differences in the abundance of numerous bacterial taxa between end stage renal disease (ESRD) and healthy individuals. ESRD patients exhibited significant expansion of bacterial families possessing butyrate-forming enzymes. Given the deleterious effects of indoxyl sulfate, p-cresol sulfate, and urea-derived ammonia, and beneficial actions of SCFA, these changes in intestinal microbial contribute to uremic toxicity and inflammation. SCFA such as butyric acid is the primary source of energy for colonocytes and is thus associated with maintenance of the epithelium. Sivaprakasam *et al*^[5] identified transporters for SCFA expressing both in the lumen-facing apical membrane and the serosa-facing basolateral membrane of colonic epithelium; therefore, the transporters responsible for the entry of SCFA particularly butyrate, are critical for colon health. The SCFA transporters monocarboxylate (MCT1) and sodium-coupled MCT1 provide an important link between colonic bacteria and colonic health and are obligatory for the beneficial effects of colonic bacteria and their fermentation products on colon. Butyric acid has been identified as being a key molecule in fortifying the cells of the colon as well as supporting the spaces between them by creating tight junctions. Butyric acid also supports in the production of key antimicrobial peptides in the mucous lining the colon walls to prevent damage by uremic toxins accumulated in CKD^[1].

This review will provide an overview of the beneficial efficacy of endophytically fermented aloe propionic-, butyric acid, and aloin in *Aloe* plants to CKD and uremic toxicity.

EFFECTS OF GUT MICROBIOME IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND GUT-DERIVED UREMIC TOXINS

In patients with chronic kidney disease (CKD), many metabolites of gut microbiota retain in the body as uremic toxins. In CKD, the accumulation of gut microbiota-derived uremic toxins, such as indoxyl-sulfate (IS), p-cresol sulfate (PCS) and trimethylamine N-oxide, accelerates the progression of CKD. Reduction of the accumulation of uremic toxins through modification gut microbiota is important for the protection against renal damage. The key mechanism protecting against acute kidney injury was suggested to be reduction in inflammation mediated by an epigenetic mechanism.

Jiang *et al*^[6] evaluated differences in the compositions of fecal microbiota between 52 ESRD- patients and 60 healthy controls in southern China using quantitative real-time polymerase chain reaction and high-throughput sequencing methods. The butyrate producing bacteria, *Roseburia*, *Faecalibacterium*, *Clostridium*, *Coprococcus* and *Prevotella* were reduced in the ESRD group.

The ecophysiology, including growth requirement and responses

to environmental factors, of major propionate and butyrate producing bacteria was discussed by Louis and Flint^[7] in relation to dietary modulation of these metabolites. Li *et al*^[8] conducted 16S ribosomal DNA pyrosequencing using fecal microbiota samples and analyzed the production of serum inflammatory factors in 550 patients with chronic kidney disease (CKD) and 22 healthy control (HC) subjects. The results revealed that compared to HC subjects, patients with CKD exhibited a significant reduction in the richness and structure of their fecal microbiota. At the phylum level, compared to the HC group, patients with CKD also presented reduced abundance of *Actinobacteria* but increased abundance of *Verrucomicrobia*. Moreover, the genera *Lactobacillus*, *Clostridium* IV, *Paraprevotella*, *Clostridium sensu stricto*, *Desulfovibrio*, and *Alloprevotella* were enriched in the fecal samples of patients with CKD, while *Akkermanisia* and *Parasutterella* were enriched in those of the HC subjects. Altered levels of the microbiota genera *Parasutterella*, *Lactobacillus*, *Paraprevotella*, *Clostridium sensu stricto*, and *Desulfovibrio* were shown to be correlated with CKD disease-severity indicators, including the estimated glomerular filtration rate. Most notably, *Akkermanisia* was significantly negatively correlated with the production of interleukin-10. Li *et al*^[9] compared the gut microbiome results of 122 subjects among whom 24 patients were diagnosed with CKD5 but did not receive hemodialysis therapy, 29 patients were diagnosed with CKD5, and received hemodialysis therapy and 69 were matched healthy controls. The author established a correlation between the gut microbiome and IS and PCS levels. In comparison to healthy control, CKD5 patients exhibited a significantly higher relative abundance of *Neisseria*, *Lachnoclostridium* and *Bifidobacterium*. *Faecalibacterium* displayed a notably lower relative abundance for CKD5 patients both with and without hemodialysis than for controls. Marzocco *et al*^[10] performed a single-center non-randomized pilot study in 20 maintenance hemodialysis (MHD) patients. They received the food additive sodium propionate (SP) with a daily intake of 2x500mg in the form of capsules for 12 weeks. The SP supplementation in MHD patients reduced pro-inflammatory parameters and oxidative stress and improved insulin resistance and iron metabolism. SP effectively lowered the important gut-derived uremic toxins IS and PCS. These improvements were associated with a better quality of life. Kikuchi *et al*^[11] reported that in a diabetic patient cohort, phenyl sulfate levels significantly correlated with basal and predicted 2-year progression of albuminuria in patients with microalbuminuria. Inhibition of tyrosine phenol-lyase, a bacterial enzyme responsible for synthesis of phenol from dietary tyrosine before it is metabolized into phenyl sulfate in the liver, reduces albuminuria in diabetic mice. Together, the author suggested that phenyl sulfate contributes to albuminuria and could be used as a disease marker and future therapeutic target in diabetic kidney disease. In a prospective crossover controlled trial, 60 patients with CKD grades 3B-4 were randomly assigned by Di Iorio *et al*^[12] to two dietary regimens; (1) 3 months of free diet (FD), 6 months of very low protein diet (VLPD), 3 months of FD and 6 months of Mediterranean diet (MD); (2) 3 months of FD, 6 months of MD, 3 months of FD, and 6 months of VLPD. Compared to FD and MD, VLPD showed a lower amount of some *Lactobacillus*, *Akkermansia*, *Streptococcus*, and *Echerichia* species. MD and VLPD reduced both the total and free serum IS and PCS compared to FD. VLPD reduced serum D-lactate compared to MD and FD. MD and, to a greater extent, VLPD are effective in the beneficial modulation of gut microbiota, reducing IS and PCS serum levels, and restoring intestinal permeability in CKD patients.

II ASSOCIATION OF CONSTIPATION STATUS WITH RISK OF CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE

In a nationwide cohort of 3,504,732 US veterans with an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min per 1.73m², Sumida *et al.*^[13] examined the association of constipation status and severity (absent, mild, or moderate/severe), defined using diagnostic codes and laxative use, with incident CKD, incident end-stage renal disease (ESRD), and change in eGFR in Cox models and multinomial logistic regression models. More severe constipation associated with an incrementally higher risk for incident CKD and ESRD and with progression eGFR decline. In conclusion, constipation status and its severity were associated with a higher risk of incident CKD and incident ESRD, and progressive eGFR decline, independent of known risk factors.

Lu *et al.*^[14] assessed the risk of ESRD between CKD patients with and without constipation in a nationwide database. Over the 13-year period, the incidences of ESRD per 1000 person-years were 22.9 for constipation group and 12.2 for non-constipation group, respectively. There was statistically significant difference for cumulative incidence for ESRD between patients with and without constipation ($p < 0.0001$). In a population of newly-diagnosed CKD patients, the author observed that subjects with de novo constipation, as compared with non-constipation, have increased risk of developing ESRD. Dietary modification and some other interventions should be tried to avoid constipation. Avoidance or even shortened intervals of constipation might be helpful to lessen the progression of CKD.

III EFFECTS OF FERMENTABLE HIGH FIBER DIET SUPPLEMENTATION IN PATIENTS ON END-STAGE RENAL DISEASE AND MAINTENANCE HEMODIALYSIS

The gut microbial changes caused by CKD are thought to perpetuate systemic inflammation. Therefore, strategies aimed at modulating the gut microbiota may be helpful in reducing complications associated with CKD. Pavan^[15] investigated 24 patients with stable CKD stage III to V. Patients were randomly assigned to 2 groups: low protein diet + prebiotic + probiotic supplementation (PPS, N = 12), receiving 3 tablets of PPS daily for 6 months, and the control group receiving low protein diet only (N = 12). The declining eGFR during PPS were significantly lower than those with low protein diet only.

Laffin *et al.*^[16] performed a double-blind, parallel, randomized, placebo-controlled trial comparing dietary supplementation of high-amylose maize resistant starch type 2 (HAM-RS2) with placebo in patients with endo stage CKD. Supplementation of HAM-RS2 led to a decrease in serum urea, IL-6, TNF α , and malondialdehyde. The *Faecalibacterium* genus was significantly increased in relative abundance following HAM-RS2 supplementation and was unchanged by placebo. Khosroshabi *et al.*^[17] reported that fifty patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD) were randomly assigned to receive a diet containing high amylose diet (HAM-RS2) or placebo over 8 weeks spanning February and September 2017 in the Bahman hospital hemodialysis ward in Tabriz, Iran. It was resulted that there was significant reduction of creatinine and uric acid levels in HAM-RS2 supplemented patients when compared with control group ($p < 0.05$). Serum levels of indoxyl sulfate (IS) was not changed significantly in both HAM-RS2 treated and control patients, whereas p-cresol level was reduced significantly

during the study period in HAM-RS2 treated patients ($p = 0.039$). Administration of fermentable high fiber diet as HAM-RS2 decreased serum levels of some nitrogenous products such as serum creatinine and p-cresol as a gut derived nitrogenous product without change in IS levels in maintenance hemodialysis patients. Due to safety, without important side effects the administration of diet enriched with fermentable fiber is suitable for patients on maintenance dialysis.

Recent studies have focused on dietary approaches to favorably alter the composition of the gut microbial communities as a treatment method in CKD. Resistant starch (RS), a prebiotic that promotes proliferation of gut bacteria such as *Bifidobacteria* and *Lactobacilli*, increases the production of metabolites including SCFAs, which confer a number of health-promoting benefits. Snelson *et al.*^[18] exhibited emerging evidence that microbiota-derived metabolites can regulate the incretin axis and mitigate inflammation via expansion of regulatory T cells. Studies from animals and patients with CKD showed that RS supplementation attenuates the concentrations of uremic retention solutes, including IS and PCS. The author explored the efficacy of RS in animal models of CKD and in humans with the condition, and discussed how RS supplementation could be a promising dietary approach for slowing CKD progression.

IV PLANT-BASED DIETS IN CHRONIC KIDNEY DISEASE

Traditional dietary recommendations to renal patients limited the intake of fruits and vegetables because of their higher potassium content. However, this paradigm is rapidly changing due to the multiple benefits derived from a fundamentally vegetarian diet such as, improvement in gut dysbiosis, reducing the number of pathobionts and protein-fermenting species leading to a decreased production of the most harmful uremic toxins, while the high fiber content of these diets enhances intestinal motility and short chain fatty acids production^[19]. In the study of patients consuming diets containing potassium-rich foods, serum potassium was not increased despite the fact that the patients had relatively low potassium intake levels at baseline (≤ 4.6 mEq/L)^[20]. A pilot study showed 2 weeks of the dietary approaches to stop hypertension diet increased serum potassium by ≤ 0.6 mEq/L and did not lead to incident hyperkalemia in patient who had eGFR of 30-59 ml/min per 1.73 m² and normal potassium levels at baseline^[21]. These reports are contrary to current dogma, and they suggest that even individuals with eGFR ≤ 60 mL/min per 1.73 m² may benefit from diets high in potassium and that their residual kidney function has the capacity to buffer the potassium intake. There is growing evidence, mostly observational, that plant-based/dietary approaches to stop hypertension diets in individuals with eGFR of 30-59 ml/min per 1.73 m² may delay progression to ESRD and dialysis and may potentially improve survival. Larger prospective studies are needed to confirm these findings as well as to determine whether the benefits of plant-based diets in CKD extend to patients with diabetes.

V SYMBIOTIC EFFECT OF ALOE VERA JUICE WITH LACTOBACILLUS FERMENTUM TO UREMIC TOXINS

In the general population, consumption of fiber-rich foods can reduce serum creatinine levels and may increase eGFR in CKD patients without DM. Carvalho *et al.*^[22] searched six databases to identify clinical trials that reported fiber intake and renal outcomes (albuminuria, proteinuria, eGFR dialysis) in patients with DM. A

vegetarian dietary pattern may have a beneficial effect on the renal outcomes and the author showed that high fiber intake was related to lower incidence of CKD after six years of follow-up.

Long-term dietary intake of non-caloric water-soluble fiber, such as aloe vera gel influences the structural and activity of microorganisms in human gut. The prebiotic activity of aloe vera juice (AVJ) was assessed by the participation of SCFAs such as acetic, lactic, and propionic acid, during 24hrs-incubation with *Lactobacillus fermentum in vitro* by Al-Madboly *et al*^[23]. From the endophytic microbiota of aloe vera gel in the fermented media, the following microbiota was identified: *Bacillus cereus*, *B.licheniformis*, *Lactobacillus paralimentarium* and *Clavispora lusitaniae*. Butyric acid was identified by GC/MSD analysis from ether extract of the gel fermentation broth^[24]. An innovative concept of symbiotics: a combination of AVJ and microbiota is a perspective on alleviation of cancer disease and improvement of gastrointestinal health by butyrate fermentation^[25]. Growing evidence has reviewed by Li *et al*^[26] that SCFAs exhibited positive effects on kidney disease in both experimental animals and patients. Regulation of SCFAs to improve kidney function can decrease the disruption of epithelial tight junction. After getting absorbed in blood, SCFAs can suppress oxidation stress by increasing superoxide dismutase, catalase, and reduced glutathione, and by decreasing nitric oxide and reactive oxygen species, which can lead to the decline of renal fibrosis and amelioration of tubular damage. SCFAs can also inhibit apoptosis by promoting autophagy and suppressing inflammation by regulating immune system, thereby decreasing serum creatinine as well as blood urea nitrogen to improve renal function. Regulation of SCFAs on blood pressure and plasma glucose may help to ameliorate renal function in chronic kidney diseases.

VI RENAL-PROTECTIVE EFFECT OF ALOE VERA, A. ARBORESCENS AND ALOIN TO UREMIC TOXINS

Chronic kidney disease (CKD) is typically detected by measuring serum creatinine levels to calculate the glomerular filtration rate (GFR) and by measuring the urinary albumin/creatinine ratio to detect proteinuria. Although the most common causes of CKD are diabetes and hypertension, the disease can be many other conditions. Creatinine clearance calculated from creatinine concentrations in urea and plasma samples, and the urine flow rate, as well as urea clearance, is used to determine the GFR of the kidney. Generation of creatinine is determined by muscle mass and diet. Thus, plasma concentrations of creatinine and urea could be used as indicators of nephrotoxicity.

Aluminium is a known potent environmental nephron-toxin causing progressive biochemical changes in the kidney. Mahor *et al*^[27] evaluated the nephron-protective effect of *Aloe vera* and aloin in aluminium sulfate ($Al_2(SO_4)_3$) exposed rats for a period of 45, 90 and 180 days. Serum creatinine, urea and uric acid levels were found to significantly increased after treatment of $Al_2(SO_4)_3$ in group II to compared to control group I animals fed with normal diet. Co-treatment with $Al_2(SO_4)_3$ and *Aloe vera* extract (group III) and $Al_2(SO_4)_3$ and aloin (group IV) showed significant decreased in creatinine, urea and uric acid. The result demonstrated that *Aloe vera* and aloin was effective in reducing aluminium toxicity in kidney. The potential of aloin treatment to reduce renal damage induced by cecum ligation and puncture (CLP) surgery in mice was measured by Lee *et al*^[28] by assessment of serum creatinine, blood urea nitrogen,

lipid peroxidation, total glutathione, glutathione peroxidase activity, catalase activity, and superoxide dismutase activity. Post-treatment with aloin resulted in a significant reduction in the deleterious renal functions by CLP, such as elevated BUN, creatinine, and urine protein. Moreover, aloin inhibited nuclear factor- κ B activation and reduced the induction of nitric oxide synthase and excessive production of nitric acid. Plasma concentration of creatinine and urea could be used as indicators of nephrotoxicity. Tanomand *et al*^[29] examined effect of alcoholic extract of aloe vera gel on kidney in adult mice treated with ethidium bromide. The author concluded that aloe vera gel, in dose dependent forms, can reduce urea, uric acid, creatinine, and tissue modification of kidney in animals with multiple sclerosis.

The function and structure of kidney may be affected by changes in the levels of insulin and diabetic kidney exhibits characteristic changes leading to renal insufficiency or complete kidney failure. Serum urea and creatinine levels were higher in diabetic rats in comparison to healthy rats. The administration of aloe vera gel extract and glibenclamide decreased serum urea and creatinine levels in comparison to diabetic controls. Only aloe vera gel extract showed improvement both in histological and biochemical parameters and suggested a protective effect of aloe vera gel on mild damage caused by type2 diabetes on kidney tissue^[30].

Quantitative analysis of phenolic compounds in *Aloe arborescens* fermented extract revealed that barbaloin concentration was found to be 14ppm by HPLC analysis. Seven known phenolic compounds and SCFAs such as acetic-, lactic-, propionic-, and butyric acid were identified by HPLC and GC/MSD analysis, respectively. Dietary intake of extract fermented by endophytic microbiota in *A. arborescens* leaves provides for beneficial influences to human health maintenance^[31]. Thus, fermented extract of *A. vera* and *A. arborescens* could be used as adjuvant therapy for the prevention and management of renal injury.

SUMMARY

CKD is a global health problem that brings to a substantial risk for end-stage renal disease, cardiovascular disease, and death. In CKD, the accumulation of gut-microbial derived uremic toxins, such as indoxyl- and p-cresol sulfate accelerates the progression of CKD and mortality. Gut microbiota has been recognized as an important endogenous organ. The kidney-gut axis would contribute to gut dysbiosis which might worsen CKD. The interest in butyrate producing endophytic bacteria in aloe plants has recently increased. Aloe vera and aloin exhibited renal protective effects *in vivo*.

European Food Safety Authority announced in "Safety of hydroxanthracene (HA) derivatives for use in food" on 2018 that maximum daily exposure to HA of aloin A+B was estimated up to 0.72 mg/kg body weight, per day, corresponding to 51 mg/person per day for a 70 kg adult^[32]. Owing to the laxative properties, the presence of aloin in the preparations intended for use in foods is controlled and limited by adding purification steps in the manufacturing process of products intended for use in foods. International Aloe Science Council (IASC) has established a quality standard for their certification program of not more than 10ppm (10mg/kg) aloin A+B for all aloe vera leaf juice (AVJ) in gradients for use in products intended for oral consumption. Constipation, commonly seen in CKD, was one of the clinical present of gut dysbiosis. IASC certificated AVJ having the laxative properties and endophytic bacteria which produce butyric acid, could plays a pivotal role to CKD patients.

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