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REVIEW

## Possible Prophylaxes of Aloe Vera Gel to Congenital Heart Disease: Case Reports

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### ABSTRACT

Our health span is to a great extent epigenetically determined by diets, gut environment, lifestyle, and various other environmental factors. Health benefits of long-term ingestion of aloe vera gel with immune modulation of the intestinal microbiota were discussed on congenital heart disease and heart failure. In this review, we demonstrated prophylaxes roles of successive ingestion of aloe vera juice on heart failure. Furthermore we presented three case reports on heart failure patients with aloe vera juice adjuvant.

**Key words:** Prophylaxis of aloe vera; Epigenetic regulation of heart failure; Congenital heart disease

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### INTRODUCTION

Congenital heart disease (CHD) is the leading cause of infant morbidity in the world, but only in the past ten years has its etiology been understood. Recent studies have uncovered the genetic basis for some common forms of the disease and provided new insight into how the heart develops and how dysregulation of heart development leads to disease. Pulmonary arterial hypertension (PAH) of variable degree is commonly associated with adult CHD. Depending on size and location of the underlying cardiac defect as well as on repair status, PAH may present with or without reversed shunting and associated cyanosis (i.e., Eisenmenger syndrome, ES). Paul-Diller and Gatzoulis<sup>[1]</sup> reviewed available data on etiology, clinical presentation, prognosis, and management strategies of PAH in adult patients with CHD. The authors discussed the numerous complications associated with ES, representing a multisystem disorder and presented general management strategies and emerging disease-treating therapies. As disease-targeting therapies, the authors exhibited that inhalation of nitric oxide has been shown to reduce total pulmonary vascular resistance in 30% of patients with ES. The same group showed more recently that responsiveness to inhaled nitric oxide (NO) is associated with a midterm survival benefit in patients with PAH and CHD.

Chronic fatigue syndrome (CFS) remains an elusive health problem, despite of increasing medical and therapeutic studies. Because of no simple test for CFS and diagnosis on clinical evaluation, no single cause for CFS is known and it is generally accepted that CFS develops through the exposure of many convergent factors.

The efficacies of aloe vera as a super-nutrient to immune<sup>[2]</sup>, oxidative stress<sup>[3]</sup>, and CFS were presented as followings: Aloe vera on bioavailability of vitamin C, E, and B<sub>12</sub><sup>[4,5]</sup>; Efficacy of acemannan, a complex carbohydrate derived from aloe vera gel to immune adjuvant, natural killer cells activity, and macrophage activation by increasing the level of NO synthase at the level of

transcription<sup>[6,7]</sup>; Control of the NO/ONOO-cycle as the central cause of heart failure<sup>[8]</sup>; Efficacy of aloe vera gel with L-arginine on nitro oxide production<sup>[9]</sup>; Prophylaxes of aloe vera gel juice alone or the juice with L-arginine to chronic fatigue syndrome<sup>[10]</sup> and with CoQ<sub>10</sub> to enhance muscle performance<sup>[11]</sup> in a survey of a large number of subjects by questionnaire.

In this review, a putative prophylactic role of aloe vera juice supplement was described to suggest that aloe vera juice supplement may be beneficial for patient with CHD as an immune modulatory. Furthermore we discussed the heart-gut axis on aloe vera gel; new target for atherosclerosis and CHD therapy and presented case reports on CHD.

## PREVENTION OF ALOE EXTRACT TO CARDIOVASCULAR AND CEREBROVASCULAR DISORDERS

Calcium<sup>2+</sup> was measured with Ca<sup>2+</sup>-selective electrodes in calcitropic CAM plants; *Aloe* spp., and *Crassula* spp. by Meyer and Popp<sup>[12]</sup>. Several organic acid anions (citrate, isocitrate, malate, and malonate) were tested for their capacity to chelate Ca<sup>2+</sup> in solution at pH 4.8. Cardiac stimulant activity of *Aloe saponaria* extract was demonstrated and calcium (+)-isocitrate isolated and synthesized stereoisomer was shown on isolated guinea pig atria<sup>[13]</sup>. Verma *et al*<sup>[14]</sup> investigated the cardio-protective activity of *Aloe vera* gel on contractile in myocardial force and coronary flow.

Five thousand patients of atheromatous heart disease, presented as angina pectoris were studied by Agarwal<sup>[15]</sup> over a period of five years. After adding the 'Hask of isabogol (*Plantago ovata* seeds) and Aloe vera gel' to diet, a marked reduction in total serum cholesterol, serum triglycerides, fasting and post prandial blood sugar level in diabetic patients, total lipids and also increase in HDL, were noted. Simultaneously the clinical profile of these patients showed reduction in the frequency of angina attacks and gradually, the drugs, like verapamil,  $\beta$ -blockers and nitrites, were tapered. The exact mechanism of the action of the two substances is not known, but it appears that probably they act as prebiotics due to their high carbohydrate contents.

### Renal protective effect of barbaloin to uremic toxins and deleterious renal damages

The effect of barbaloin on cardiac electrophysiology was investigated by Cao *et al*<sup>[16]</sup>. Cardiac action potentials and ionic currents were recorded in isolated rabbit ventricular myocytes using whole-cell patch-clamp technique. Additionally the antiarrhythmic effect of barbaloin (200 $\mu$ mol/L) was examined in Langendorff-perfused rabbit hearts. Barbaloin significantly inhibited aconitine- induced ventricular arrhythmias. These results demonstrated that barbaloin has potential as an antiarrhythmic drug.

Barbaloin has a myocardial protective effect. The endoplasmic reticulum stress (ERS)-mediated apoptosis pathway serves an important role in the pathogenesis of myocardial ischemia-reperfusion injury (MIRI). Inhibiting ERS may significantly improve the progression of MIRI and serve a role in its prevention. Therefore, based on current knowledge of ERS-mediated cardiomyocyte apoptosis and cardioprotective effect of barbaloin, the study by Cui *et al*<sup>[17]</sup> evaluated the myocardial protective effect and potential mechanisms of barbaloin pretreatment in MIRI in a rat model. Barbaloin pretreatment may attenuate MIRI by inhibiting the CNPY2-PERK apoptotic pathway.

### Probiotic administration in congenital heart disease: a pilot study

Necrotizing enterocolitis (NEC) is predominantly a disease of premature infants. Among term infants, the prevalence of NEC has been estimated at 1 in 20,000 live births. Congenital heart disease (CHD) is one of the most consistent risk factors for NEC in term infants. Ellis *et al*<sup>[18]</sup> investigated the impact of probiotic *Bifidobacterium longum* ssp. *infantis* on the fecal microbiota and plasma cytokines in neonates with congenital heart disease. Sixteen infants with CHD were randomly assigned to receive either *B.infantis* or placebo for 8 weeks. Healthy control infants had increased total bacteria, total *Bacteroidetes* and total *Bifidobacteria* compared to the infants with heart disease, but there were no significant differences between the placebo and probiotic groups. Plasma IL10, IFN- $\gamma$  and IL 1 $\beta$  levels were transiently higher in the probiotic group. CHD in infants is associated with dysbiosis. Probiotic *B.infantis* did not significantly alter the fecal microbiota. Alterations in plasma cytokines were found to be inconsistent.

## DIAGNOSIS AND MANAGEMENT OF NON-CARDIAC COMPLICATIONS IN ADULTS WITH CONGENITAL HEART DISEASE

Life expectancy and quality of life born with congenital heart disease (CHD) have been greatly improved over the past 3 decades. While representing a great advance for these patients, who have been able to move from childhood to successful adult lives in increasing numbers, this development has resulted in an epidemiological shift and a generation of patients who are at risk of developing chronic multisystem disease in adulthood. Non-cardiac complications significantly contribute to the morbidity and mortality of adults with CHD. Reduced survival has been documented in patients with CHD with renal dysfunction, restrictive lung disease, anemia, and cirrhosis. Furthermore, as this population ages, atherosclerotic cardiovascular disease and its risk factors are becoming increasingly prevalent. A scientific statement from the American Heart Association was provided by Lui *et al*<sup>[19]</sup> as a state-of-the-art update of non-cardiac complications in adults with CHD.

## DIETARY FIBER FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

Certain dietary habits can promote alteration of gut microbiota and are causally responsible for heart disease. Elevated plasma levels of choline, betaine, deriving from a protein-enriched diet, are correlated with the progression of atherosclerosis and increased risk for cardiovascular disease (CVD). In contrast, Mediterranean diet and dietary fibers modulating gut microbiota composition and short-chain fatty acids (SCFAs) production exert a protective effect against CVD. The SCFA butyrate has a pivotal role in protecting heart from pathologic hypertrophy and ischemia. Paparo *et al*<sup>[20]</sup> reviewed evidence on the important of diet and of gut microbiota in CVD.

## EPIGENETIC REGULATION OF HEART FAILURE

Heart failure (HF) is a complex syndrome affecting millions of people around the world. Liu and Tang<sup>[21]</sup> presented the role of DNA methylation, post-translational modification of histones, adenosine triphosphate-dependent chromatin conformation and remodeling, and non-coding RNAs in HF pathophysiology. The authors reported epi-

genomic studies on human and animal models in HF.

### Gut microbiota-derived short chain fatty acids in children with congenital anomalies of the kidney and urinary tract

Congenital anomalies of kidney and urinary tract (CAKUT) are the leading cause of chronic kidney disease (CKD) in children. Since gut microbiota and their metabolite short chain fatty acids (SCFAs) have been linked to CKD and hypertension, Hsu *et al.*<sup>[22]</sup> examined whether gut microbial composition and SCFAs are correlated with blood pressure (BP) load and renal outcome in CKD children with CAKUT. The authors enrolled 78 children with CKD stage G1-G4. Up to 65% of children with CAKUT had BP abnormalities on 24h ambulatory blood pressure monitoring. CKD children with CAKUT had lower risk of developing BP abnormalities and CKD progression than those with non-CAKUT. Reduced plasma level of propionate was found in children with CAKUT, which was related to increased abundance of phylum *Verrucomicrobia*, genus *Akkermansia* and species *Bifidobacterium bifidum*. CKD children with abnormal ambulatory BP monitoring profile had higher plasma levels of propionate and butyrate. These findings highlight that gut microbiota-derived SCFAs like propionate and butyrate are related to BP abnormalities in children with an early stage of CKD. Early assessments of these microbial markers may aid in developing potential targets for early life intervention for lifelong hypertension prevention in childhood CKD.

### Beneficial roles of aloe fermented butyrate, propionate, and aoin to chronic kidney disease and uremic toxins

Chronic kidney disease (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 accelerates the progression of CKD and mortality. 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. Koizumi *et al.*<sup>[23]</sup> exhibited renal protective effect of aloe plant extract and aoin to chronic kidney disease and uremic toxins.

## THE HEART-GUT AXIS; NEW TARGET FOR CONGESTIVE HEART FAILURE THERAPY

### A role for the gut microbiome in the pathogenesis of heart disease

Several mechanisms for the potential role of microbiome and bacterial translocation that may contribute to the pathogenesis of cardiovascular disease and serve as targets for therapeutic approaches was discussed by Forkosh and Ilan<sup>[24]</sup>. Alteration in the gut microbiota is being explored as a method of reducing risk factors associated with cardiac disease.

## THE ROLES OF MICRORNAS IN CONGENITAL HEART DISEASE

### MicroRNAs in congenital heart disease biomarkers and heart development

Congenital heart disease (CHD) is a broad term which encompasses a spectrum of pathology; the most common phenotypes include atrial septal defects, ventricular septal defects, patent ductus arteriosus and tetralogy of Fallot. The impact of CHD is profound and it is estimated to be responsible for over 40% of prenatal deaths. MicroRNAs (micRs) are small, highly conserved, non-coding RNAs which have complex roles in a variety of pathophysiological states. MicRs are

post-transcriptional negative regulators of gene expression. Individual micRs are known to exert effects in multiple target genes therefore the altered expression of a single micR could influence an entire gene network resulting in complex pathological states. Recent evidences suggest a role in the dysregulation of micRs in CHD. Smith *et al.*<sup>[25]</sup> investigated current knowledge of the cause-effect relationships of micRs in CHD and presented their potential as therapeutic targets and biomarkers in this clinical setting.

### MicroRNAs in muscle gene therapy

MicroRNAs (micRs), a small non-protein-coding RNAs, are able to post-transcriptionally regulate many genes and exert pleiotropic effects in the muscle. Deleterious changes in micR expression play an important role in muscle diseases. MicRs are possible therapeutic targets, and micR-based gene therapy for smooth, skeletal, and cardiac muscles is an extremely interesting field for harnessing the complexity of micR-based therapeutic approaches. Rotini *et al.*<sup>[26]</sup> reviewed the recent literature on key micR targets to treat skeletal, cardiac, and smooth muscle diseases and novel valuable clinical tools for more effective treatment strategies in muscle degeneration.

### MicRNA and reactive oxygen species crosstalk in cardiac and pulmonary disease

Reactive oxygen species (ROS) affect many cellular functions and the proper redox balance between ROS and antioxidants contributes substantially to the physiological welfare of the cell. MicRNAs regulate gene expression at the post-transcriptional level contributing to all major cellular processes, including oxidative stress and cell death. Several micRNAs have been reported to crosstalk with oxidative stress in both cardiac and pulmonary systems. Climent *et al.*<sup>[27]</sup> summarized the findings for the ten micRNAs shared by cardiac and pulmonary settings. Three of them, micR-155, micR-21, and micR1/206, have been extensively studied in cardiac and pulmonary diseases.

## CARDIOPROTECTIVE EFFECT OF ALOE VERA, BARBALOIN, AND SODIUM BUTYRATE

In vivo models of ischemia-reperfusion injury are commonly employed to evaluate the cardioprotective activity of aloe vera. Aloe vera administered with gastric gavage previous to abdominal aorta and spinal cord ischemia increased antioxidant enzymes activity (SOD, CAT and GPX) and reduced lipid peroxidation level (MDA content), edema, hemorrhage, and inflammatory cell migration in Wistar albino rats. Furthermore, the oral gavage administration of aloe vera (30 mg/kg/day for one month) resulted to decrease ischemic fiber degeneration by preventing the formation of lipid peroxides, increasing antioxidant enzymes, and up-regulating the transcription factor nuclear respiratory factor 1 in Wistar albino rats<sup>[28]</sup>.

Barbaloin (20 mg/kg/day, 5 days) administered intragastrically reduced myocardial oxidative stress and inflammatory response and increased adenosine monophosphate-activated protein kinase (AMPK) signaling in sprague-dawley rats in a myocardial ischemia/reperfusion injury<sup>[29]</sup>.

Treatment of apolipoprotein-E knockout mice with sodium butyrate slowed the progression of atherosclerosis in the aorta by reducing adhesion and migration of macrophages and increasing the stability of the plaque. It also reduced oxidative and inflammatory events at the lesion site by decreasing NADPH oxidase and decreasing NFκB activation<sup>[30,31]</sup>.

## A CASE REPORT OF CONGENITAL HEART DISEASE

### Case report 1: The risk remission for the congenital heart disease in 30-years female

A 30-years female who took four times-surgery (Fontan procedure) to congenital heart disease (CHD) after her birth 45- days, on 3-years-old, five-years-old and seven-years-old, showed SpO<sub>2</sub> about 80% (cyanosis) and high level of uric acid value, and had a relapse into the CHD on Nov. 2012. The blood examination showed high levels on hemoglobin, hematocrit and BNP, and low level of GFR. She does not have surgery again and ingested aloe vera juice since then to Jan. 2014. The blood examination recovered into normal standard levels on 2015. She spends well QOL with successive AVJ ingestion and got married.

### Case report 2: The risk remission for the angina pectoris in 44-years female

A 44-years-old female who took an open heart surgery on 1995, was administered azilsartan and carvedilol. And she took several times balloon-catheter-treatments during 1994-2010. She started to take aloe vera juice 1000ml/d on 2010 without any antihypertensive drug. She has no constipation and spends well QOL with successive AVJ ingestion during 2010-2020.

### Case report 3: The risk remission for the congenital heart disease: intraventricular septal defect, in 44-years female

A 44-years-old female who took surgery in her child, was restricted from physical exercise in high school days. She took rheumatoid arthritis and felt vertigo and heart palpitation on 20-years old. She was hospitalized from pericarditis due to stress on 40-years old. On 41-years-old she started to ingest aloe vera juice 500ml/d with CoQ<sub>10</sub> 160-240mg/d. Since then she was well recovered without constipation and spent well QOL. Aloe vera juice ingestion with CoQ<sub>10</sub> exhibited no rheumatoid arthritis and heart disease syndrome without drug administration.

## DISCUSSION

The composition of the gut microbiota in people with heart failure is different from those with healthy status. Chronic kidney disease (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 accelerates the progression of CKD and mortality<sup>[23]</sup>. Gut microbiota has been recognized as an important endogenous organ. A reduction in short chain fatty acids-producing bacteria in patients with heart failure might be a notable characteristic for patients with heart failure.

## SUMMARY

Aloe vera gel reduced urea, uric acid, creatinine and tissue modification of kidney in animal with multiple sclerosis. And endophytically fermented propionate and butyrate in aloe vera gel improved kidney function and gut-microbial ecosystem in host<sup>[32]</sup>.

In case reports on congenital heart disease we presented possible prophylaxes benefits of the successive ingestion of aloe vera juice, and well QOL.

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