

## Epigenetic Roles of Microbiota and Aloe vera in Health and Disease

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### ABSTRACT

Our healthspan is to a great extent epigenetically determined by diets, lifestyle, and various other environmental factors. Gut microbiota has been proven to be the major player in maintaining human health. Our previous report described health benefits of long-term ingestion of aloe vera gel through the modification of the intestinal microbiota. In the present review, we broadly cover the topics of microbiota and aloe vera gel ingestion related to attenuation of reactive oxygen species, prevention of cardiovascular disorders, effects of life-prolonging calorie restriction. Additional data are summarized on prophylactic actions of fermented butyrate, and aloe-emodin related components against obesity. Prophylactic actions of aloe vera gel on healthy aging, skin photo-aging, and the viability and lifespan in *Drosophila melanogaster* are discussed in relation to the properties

of butyrate and its potential effects involved in health and disease.

**Key words:** Aloe vera gel ingestion; Microbiota interaction; Anti-obesity; Calorie restriction; Healthy aging; Longevity

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### INTRODUCTION

It has been shown that long-term aloe vera ingestion increases longevity and suppresses the occurrence and severity of age-related diseases of laboratory animals. More importantly, it attenuates the age-associated functional declines without any harmful or deleterious side effects in these animals as reported by the laboratory of one of us (BPY)<sup>[1]</sup>. Chandrashekar *et al*<sup>[2]</sup> and Yagi<sup>[3]</sup> reported that health maintenance with aloe vera in long-term ingestion is influenced by the intestinal microbiota during aging. Rahmani *et al*<sup>[4]</sup> described possible mechanisms of action and therapeutic implications of aloe vera in health maintenance. However, the major mechanism underlying such beneficial effects has not been established. The aloe vera's anti-aging action was more discernible in the skin aging. For instance, the study done by Cho *et al*<sup>[5]</sup> on 30 healthy women aged 45 years or older found that consuming aloe vera gel improves skin elasticity, boosts collagen production, and significantly reduces wrinkles. Although the study was done with a small group, the author's data clearly indicate that dietary aloe vera gel could exert various anti-aging benefits of the skin.

Disturbance in the gut microbiota is known to associate with development of many diseases. Various nutraceuticals including probiotics, prebiotics and aloe vera are known to enhance gut microbial homeostasis, thus reducing the deleterious effects of pathogenic organisms as well as the pro- inflammation potential. It was reported that the aloe vera gel leads to increased fermentation and promotes the bacterial growth as shown by Chiodelli *et al*<sup>[6]</sup>. The authors also reported the growth of lactic acid bacteria after fermentation of aloe vera gel, thus raising the opportunity of the

probiotic effect of aloe vera. In our earlier paper, we identified butyrate, from *in vitro* fermentation by endophytic bacteria, *Lactobacillus* and *Bacillus* species, in aloe vera gel<sup>[7]</sup>. Fakhry *et al*<sup>[8]</sup> isolated a total of 25 spore-formers from feces and ileal biopsies of healthy human volunteers and identified various species. The authors characterized spore-former bacteria able to colonize the human gastrointestinal tract (GIT). Plant roots and GIT are similar in multiple ways including nutritional absorptive functions, and the site of diverse microbial colonization in an-aerobic conditions. These same authors found that sequence comparisons between GIT and plant root isolates using multiple genes, implying that human and plant isolates are closely related strains. Therefore, it is likely that much of the GIT microbes may be acquired by consumption of foods bearing microbes, *Bacillus* species, in plants. The presence of *Bacillus* species in human intestinal tract was evaluated through isolation of *Bacillus* from mucosa derived from intestinal resection from 20 males and females aged 18 to 88 years by Torrens *et al*<sup>[9]</sup>. Sequence comparisons of *Bacillus* strains between human and plant root isolates using multiple genes indicated that human and plant isolates are closely related strains. *Bacillus* species have adapted to life within the GIT and should be considered gut commensals rather than solely soil microorganisms, as consumption of microbes in plants may be one of the major routes by which human gut microbiome becomes established.

## WIDE BENEFITS OF ALOE VERA AND ITS INGREDIENTS

Aloe vera gel is commercially used in cosmetics as well as food supplements because of its multiple efficacy. One of such effects is the inhibitory action on various enzymes. Sacan *et al*<sup>[10]</sup> tested it out on elastase, neuraminidase,  $\alpha$ -amylase, and lipase. Their results showed that aloe vera extracts exhibit a high inhibitory action against elastin and  $\alpha$ -amylase activities, and mild inhibition on neuraminidase and lipase activities. In addition, the antioxidant activities of aloe vera leaf skin and gel extract were detected with the help of the use of reducing agent, DMPO, and NO radical scavenging activity. Therefore, aloe vera gel could potentially be used as a source of natural elastase and  $\alpha$ -amylase inhibitory activities and antioxidant activity in pharmaceutical, cosmetic and food industries. Regarding aloe's antioxidant capability, Lim *et al*<sup>[11]</sup> showed that lifelong dietary aloe vera supplementation in aged rats had superior anti-oxidation action against lipid peroxidation, while boosting superoxide dismutase (SOD) and catalase activity.

Bala *et al*<sup>[12]</sup> evaluated the possible radio-protective potential of aloe vera extract against whole-body X-ray irradiation-induced testicular alterations in male balb/c mice. X-ray irradiation resulted in elevation of the levels of reactive oxygen species, lipid peroxidation, a reduction in glutathione concentration, but interestingly, enhanced activities of antioxidant enzymes such as glutathione reductase, glutathione peroxidase, catalase, SOD and glutathione-S-transferase. The protective action of aloe vera was documented as irradiated animals pre-treated with aloe vera extract revealed an improvement in antioxidant status, inhibition of lipid peroxides, apoptotic cell formation and enhanced testicular parameters compared to the X-ray-exposed group. Aloe vera extract could ameliorate X-ray-induced damage due to its free radical scavenging properties and its potential to boost cellular antioxidant defense machinery.

Recently the protective effect of aloe vera extract against bisphenol A (BPA) was reported. BPA is a potential endocrine-disrupting chemical because it has the capability to imitate the activity of natural

estrogen and among numerous harmful effects it is considered as a potent risk factor for infertility because it induces testicular toxicity. Behmanesh *et al*<sup>[13]</sup> analyzed the protective effect of aloe vera on tissue and oxidative stress in male rats. BPA significantly decreased body weight as well as testis weights. Seminiferous tubule diameter and height of seminiferous epithelium were decreased significantly in groups receiving BPA compared to the control. Thus, it appears that aloe vera gel extract could be used as a protective agent against the harmful BPA and its toxicity, for example, in BPA-containing can lining materials for food-containers.

Protective effect of aloe vera gel polysaccharides (APs) on pancreatic  $\beta$ -cells in response to free fatty acids (FFA) was determined using hamster pancreatic  $\beta$ -cells line HIT-T15 by Kim *et al*<sup>[14]</sup>. It was found that the anti-apoptotic properties of APs were largely due to the relief of endoplasmic reticulum (ER) stress signaling. APs were effective in interfering with the FFA-induced activation of the PERK and IRE-mediated pathways as well as ROS generation, thereby protecting pancreatic  $\beta$ -cells from lipotoxicity. After oral administration of APs, markedly lowering fasting blood glucose levels were observed in db/db mice, providing evidence of the potential of APs as an alternative insulin sensitizer. Therefore, it seems that APs have a protective effect against type 2 diabetes by modulating obesity-induced ER stress in pancreatic  $\beta$ -cells.

## PREVENTION OF CARDIOVASCULAR DISORDERS BY ALOE VERA

Coronary heart disease causally associated with the accumulation of blood lipids in the lining of the arteries is one of the major causes of death. The ingestion of aloe vera gel may have beneficial effects by lowering blood cholesterol, triglycerides, and phospholipids that accumulate in the large and medium-sized arteries, including the coronary arteries. In our previous papers, prevention of cardiovascular and cerebro-vascular disorders by aloe species were reviewed<sup>[3]</sup>. Agarwal<sup>[15]</sup> conducted the prevention of heart disease study with 5,000 atheromatous patients over a period of five years. Addition of husk of isabogol (*Plantago ovata* seeds) and aloe vera to diet markedly reduced total serum cholesterol, serum triglycerides, fasting- and postprandial blood sugar levels in diabetic patients with concomitantly increased HDL. The clinical profiles of these individuals showed a reduction in the frequency of angina attacks and the intake of drugs, like verapamil,  $\beta$ -blocker and nitrites, were gradually tapered off. One notable outcome of the study was that no untoward side effect of the dietary supplements was detected. Aloe vera beverage intake was found to affect lipid metabolism by decreasing total cholesterol, and triglycerides as important biomarkers of cardiovascular disease, and increasing HDL cholesterol. Interestingly, aloe vera juice intake also was reported to decrease angina pectoris frequency and relaxed chest pain caused by cardiac oxygen deficiency<sup>[10,16]</sup>.

Zheng *et al*<sup>[17]</sup> systematically assessed the effects of external application of aloe vera for the prevention and treatment of infusion phlebitis. Twenty-two trials with 5,546 participants were involved in prevention studies of aloe vera for phlebitis, and an additional 21 trials with 1,919 participants were involved in the treatment of phlebitis. However, there is no clear-cut evidence obtained, requiring further systemic investigation. Chemotherapy-induced phlebitis (CIP) not only causes new health hazards to the patients, but also affects the implementation of chemotherapy. *Aloe vera* has been frequently used for the prevention and treatment of CIP in clinical practice. Gao *et al*<sup>[18]</sup> evaluated the clinical value of aloe vera for the prevention and

treatment of CIP. The results show that aloe vera significantly reduced the occurrence of second and third-degree phlebitis compared with the control group.

## THE PUTATIVE MICROBIOTA MODIFICATION BY HEALTH-PROMOTING CALORIE RESTRICTION

Calorie restriction (CR) without malnutrition is epigenetically most powerful anti-aging intervention with the increased not only median, more importantly, also maximum lifespan in all experimental organisms tested to date. The beneficial CR was observed also in monkeys and humans. One unique aspect of CR is its most potent and diversified anti-oxidative defense system, thereby suppressing oxidative stress-induced chronic inflammation that underlies many chronic diseases. If aging is caused by increased free radical damage and weakened defense system, as happen under oxidative stress, elimination of free radicals and/or boosting defense against oxidative stress should exert beneficial effects against organism's aging process<sup>[19]</sup>. One such attempt was launched by Mathur *et al*<sup>[20]</sup>, who examined the effect of larval diet supplementation on longevity with five different concentrations of aloe vera gel on short-lived adult *Drosophila melanogaster* populations. Aloe vera gel supplement of larval diet extended adult longevity in both male and female flies without reducing fecundity. In addition, the authors found the efficient reactive oxygen species scavenging through increased antioxidant enzymes activity and better neuroprotection as indicated by increased locomotor activity in adult male flies.

For human study of CR, Redman *et al*<sup>[21]</sup> with 53 non-obese adults (34 CR and 19 control), reported that energy expenditure and several endocrine mediators are reduced with CR regimen. Findings from this 2-year CR trial in healthy, non-obese human subjects provided evidence of metabolic slow-down accompanied with reduced oxidative stress, which is in line with the oxidative stress hypothesis of aging. CR elicits benefits for healthspan extension with decreased risk of cardio-metabolic disease (CVD). Most *et al*<sup>[22]</sup> investigated whether CR can reduce risk factors for CVD and insulin resistance in non-obese humans, and assessed whether improvements are exclusive to a period of weight loss or continue during weight maintenance. They concluded that sustained CR in healthy, non-obese individuals is beneficial for reducing risk factors of cardiovascular and metabolic diseases, ectopic lipid accumulation, blood pressure, and lipid profile, while improving insulin sensitivity. Das *et al*<sup>[23]</sup> evaluated the effect of a 2-year CR regimen on body composition of human subjects including the influence of gender and human body mass index (BMI) of participants enrolled in Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2, a multicenter, randomized controlled trial. It was found that two years of CR produced the positive impacts on both whole-body and regional adiposity. Data on fat-free mass (FFM) were commensurated with the reduced body mass, although men in the CR group lost more FFM than the women did, the percentage of FFM in the men in the CR group was higher than at baseline. CALERIE was registered at clinicaltrials.gov as NCT00427193.

Environmental stresses experienced during development exert many long-lasting effects on health and disease status. In some cases, the beneficial effects of low-dose oxidants are attributed to adaptive protective mechanisms of mitochondria called mitohormesis, with increased anti-oxidative defense enzymes through the enhanced expression of stress response genes. For instance, Obata *et al*<sup>[24]</sup> showed that the transient exposure to low concentrations of oxidants

during development in *Drosophila* leads to an extension of adult lifespan, which is a typical hormetic response. This phenomenon depends upon oxidants acting in an antibiotic-like manner to deplete selectively the microbiome of *Acetobacter* proteobacteria. These authors were able to show that the presence of *A. species*, such as *A. aceti*, in the indigenous microbiota increases age-related gut dysfunction and shortens lifespan. Their study demonstrates that low-dose oxidant exposure during early life can extend lifespan more likely due to microbiota modification rather than mitohormesis.

## MICROBIOTA INVOLVED IN REDUCING ADIPOSITY BY BUTYRATE AND SHORT CHAIN FATTY ACIDS

Currently obesity from an excessive calorie intake is one of the major public health threats because of its underlying cause for many chronic diseases. Obesity is recognized globally as a major mortality risk factor due to its involvement in other metabolic complications like chronic inflammation, insulin resistance and type2 diabetes. Although there is no simple solution for the complex obesity-related problems, more basic approaches could lead to physiological clues on the solution for the obesity problem. As turned out, recent emerging microbiota data pose clearly as one of the major contributors in the development of obesity.

Tsai *et al*<sup>[25]</sup> who investigated gastrointestinal tract microbiota's critical role in the development of obesity, identified lactic acid bacteria as the likely candidate responsible for the anti-obesity effect. In our previous report, we described the innovative approach on the symbiotic effect by blending *Lactobacillus fermentum* into aloe vera juice to yield lactic acid, acetic acid, and propionic acid in the fermentation extract<sup>[26]</sup>. Mollica *et al*<sup>[27]</sup> demonstrated that hepatic mitochondria were identified as the main target of the beneficial effect of butyrate in attenuating insulin resistance and fat accumulation in diet-induced obese mice. Butyrate activated the AMPK-acetyl-CoA carboxylase pathway, boosting metabolism. Butyrate that modulates mitochondrial efficiency can be a new therapeutic strategy for counteracting obesity and insulin resistance. Butyrate may prevent diet-induced obesity through increasing energy expenditure. However, it is unclear whether  $\beta$ 3-adrenergic receptors (AR $\beta$ 3) mediate butyrate-induced adipose lipolysis or not. For instance, Jia *et al*<sup>[28]</sup> reported that butyrate treatment stimulates adipose lipolysis and mitochondrial oxidative phosphorylation through histone hyper-acetylation-associated AR $\beta$ 3 activation. A short-term oral administration of butyrate is effective in alleviating diet-induced obesity through activation of the AR $\beta$ 3-mediated lipolysis in the epididymal white adipose tissue, and is beneficial for anti-obesity in mice, revealing a possibility of butyrate and its derivatives for the treatment and prevention of obesity-related metabolic disorders in humans. Aquilar *et al*<sup>[29]</sup> demonstrated the action of orally administered butyrate on adipose tissue expansion and insulin resistance using diet-induced obese Apo E<sup>-/-</sup> mice. The obese mice fed with butyrate presented a modest reduction of weight gain associated with reduction of adipocyte expansion, induction of adipogenesis and angiogenesis, and adiponectin production. Butyrate also improved insulin sensitivity by increasing insulin receptor expression associated with activation of Akt signaling pathway. These results strongly suggest that oral supplementation of butyrate reduces obesity-associated inflammation and insulin resistance in *in vitro* and *in vivo* models. In animal model of metabolic syndrome with non-alcoholic fatty liver disease, researchers have recently demonstrated that the administration of butyrate is able to reduce insulin resistance,

liver damage, dyslipidaemia through modulation of the inflammatory process. Pharmacokinetic and pharmacodynamic studies in human show that oral administration of butyrate is safe and well tolerated, thus suggesting a reasonable approach for the attenuation of insulin resistance in the obese child. Most recently, Berni Canani R.<sup>[30]</sup> initiated obesity clinical trials of butyrate on children with obesity on 2018.

Goswami *et al.*<sup>[31]</sup> explored the possible role of vagal afferents in the anorexigenic effect of short chain fatty acids (SCFAs). Intraperitoneal injection (IP) of SCFA molecules (6 mM/kg body wt) suppressed food intake in fasted mice with the rank order of butyrate>propionate>acetate. Butyrate IP induced significant phosphorylation of extracellular-signal- regulated kinase1/2, cellular activation markers, in nodose ganglia and their projection site, media nucleus tractus solitaries. Moreover, butyrate directly interacted with isolated neurons from nodose ganglia and induced intracellular Ca<sup>2+</sup> signaling. These results identified the vagal afferent as the novel pathway through which exogenous SCFAs execute the remote control of feeding behavior and possible other brain functions. Vagal afferents might participate in suppression of feeding by intestinal-born SCFAs. Whitt *et al.*<sup>[32]</sup> investigated whether histone deacetylase 3 (HDAC3) in intestinal epithelial cells (IECs) regulates metabolism and the development of obesity in mice. Butyrate significantly reduced the activity of HDAC3 in IECs of mice to prevent diet-induced obesity. The importance of HDAC3 in obesity was also seen in human subjects. The authors evaluated HDAC3 levels in 43 pediatric patient ileal biopsies relative to age-normalized patient weight, and found that HDAC3 levels in the intestine positively correlated with patient weight, which suggests dysregulation by intestinal HDAC3 may lead to alterations in body weight. Rastelli *et al.*<sup>[33]</sup> analyzed various specific complex pathways and their key interactions. For instance, the nervous routes, endocrine routes by which gut microbes communicate with host, and the key metabolites involved in such specific interactions (e.g. SCFAs) as well as their targets. Their review, focusing on the mechanisms linking microbes, obesity, and related disorders, highlighted the role of metabolic endotoxemia in the onset of metabolic disorders and the implications for alterations in gut microbiota-host interactions and ultimately the onset of diseases.

## EFFECTS OF ALOE-EMODIN RELATED COMPONENTS ON CELLULAR SIGNALING INVOLVED IN DIABETES AND OBESITY

Subash-Babu *et al.*<sup>[34]</sup> examined the effects of aloe-emodin (AE) on the inhibition of adipocyte differentiation during 3-isobutyl-1-methylxanthine- induced adipocytes differentiation in human mesenchymal stem cells (hMSCs). Using quantitative reverse transcription polymerase chain reaction, the authors studied the mRNA expression levels of resistin, adiponectin, aP<sub>2</sub>, lipoprotein lipase, PPAR $\gamma$ , and TNF- $\alpha$  in hMSCs undergoing adipocyte differentiation; treatment with AE decreased the expression of these adipogenic genes and decreased adipocyte differentiation. AE significantly inhibited hMSCs proliferation and pre-adipocyte differentiation within the first 2 days of treatment, indicating the anti-adipogenic effect. Sangeetha *et al.*<sup>[35]</sup> obtained evidence showing AE's significant insulin mimic effect favoring glucose uptake in L6 myotubes (an *in vitro* model mimicking skeletal muscle cells). AE modulates glucose uptake through activation of PI3K, an important insulin signaling intermediate. The authors discussed bioactive compounds from medicinal plants offering enhanced therapeutic

potential for the combined pathophysiology of diabetes and obesity. Alshatwi *et al.*<sup>[36]</sup> determined the protective effect of AE from high glucose induced toxicity in RIN-5F (pancreatic  $\beta$ -cell) and analyzed the restoration of its function. RIN-5F cells have been cultured in high glucose condition, with and without AE. RIN-5F treated with both high glucose and AE suppressed ROS generation and prevent RIN-5F cell from glucotoxicity. In addition, AE treated cells cultured in high glucose were transferred to standard medium, normal responsiveness to glucose was restored within 8 h and normal basal insulin release within 24 h was achieved when compared to high glucose. AE appears to possess a putative therapeutic property to overcome  $\beta$ -cell failure that occurs most of type2 diabetic patients.

Youn *et al.*<sup>[37]</sup> examined the anti-obesity effect of aloe vera barbaloin by using 3T3-L1 adipocytes. Barbaloin suppressed lipid accumulation in the process of differentiation of 3T3-L1 adipocytes. During the differentiation of 3T3-L1 adipocytes, barbaloin treatment significantly down regulated the mRNA expression of PPAR- $\gamma$  and C/EBP- $\alpha$ . It also significantly up-regulated the phosphorylation of AMPK- $\alpha$ , when examined by a western blot assay. These results indicate that barbaloin has a potent antiadipogenic effect in 3T3-L1 cells via the inhibition of adipocyte differentiation and adipogenesis. Effects of AE on hyperlipidemia rats were investigated by Ji *et al.*<sup>[38]</sup> using UPLC-ESI-QTOF-MS based urinary metabolomics. After oral administration of AE for 6 week by rats, the total cholesterol and low-density lipoprotein-cholesterol levels in 50 and 100 mg/kg of AE groups were both decreased significantly. The results indicate that AE has an efficacious effect on HFD-induced hyperlipidemia.

Anand *et al.*<sup>[39]</sup> reported the efficacy of aloe-emodin-8-O-glucoside (AEG) on alleviating insulin resistance and augmenting glycogen synthesis in L6 myotubes and 3T3L1 adipocytes. AEG was found to enhance glycogen synthesis through the inhibition of glycogen synthase kinase 3 $\beta$ . AEG enhances glucose transport by modulating the proximal and distal markers involved in glucose uptake and its transformation into glycogen.

## PROPHYLACTIC ROLES OF ALOE VERA IN VARIOUS PHYSIOLOGICAL FUNCTIONS

It is well known that obesity raises the risk of numerous health problems, including cardiovascular disease, type 2 diabetes, and some form of cancer. Lately, researchers are increasingly finding out that overweight may also have negative impacts on the brain structure, as suggested by some studies that obesity accelerates the onset and progression of brain shrinkage: the volume reduction in white and gray matter as occurring with aging.

Ronan *et al.*<sup>[40]</sup> conducted a cross-sectional analysis of magnetic resonance image-based brain structure on a population-based cohort of healthy adults. Study participants included 527 individuals aged 20-87 years. Cortical reconstruction techniques were used to generate measures of whole-brain cerebral white-matter volume, cortical thickness, and surface area. Results indicated that cerebral white-matter volume in overweight and obese individuals was associated with a greater degree of atrophy, with maximal effects in middle-age corresponding to an estimated increase of brain age of 10 years. These findings implied the possibility of adiposity as a significant risk factor underlying neurodegeneration and cognitive decline.

Obesity is implicated with many other health problems including sleep disorders. While sleep apnea and neuropathy resulting from diabetes may drastically decrease the quality of sleep, insomnia is a common side effect of medications taken for obesity-related disorders like high blood pressure and cholesterol. Abdollahnejad *et al.*<sup>[41]</sup>

investigated the sedative and hypnotic effects of the aqueous extract of aloe vera on rats. Analysis of the electroencephalography showed that there is concomitant change in rapid-eye and none rapid-eye movement sleep in parallel with the prolonged total sleeping time. Results show that the aloe extract has sedative-hypnotic effects on both functional and electrical activities of the brain, thus revealing the efficacious effects of aloe vera extract on the brain activity. The effect of aloe vera in animal models of learning and memory, depression, and locomotion was investigated by Halder *et al*<sup>[42]</sup>. To assess learning and memory, the passive avoidance task and elevated plus-maze were used. For assessment of depression, forced swim and tail suspension tests were performed, and to assess locomotor activity, the rota rod test and photoactometer were used. Results show that aloe vera (0.2 and 0.4g/kg, per oral) was found to significantly increase the acquisition and retention step-down latency as compared to control in the passive avoidance task. These findings substantiate that aloe vera ingestion enhances learning and memory, and also alleviates depression in mice.

A pilot study of Lewis *et al*<sup>[43]</sup> investigated the effect of an aloe vera polymannose multinutrient complex (APMC) formula on cognitive and immune functions of adults with Alzheimer's disease (AD). Subjects participated in an open-label trial, females (n=28) and males (n=6), and consumed 4 teaspoons per day of APMC. The APMC formula used in the study was well-tolerated among all subjects. The product showed a significant improvement in the ADAS-cognition score and demonstrated sound immune-modulator activity with noteworthy responses in cytokines and several lymphocytes and monocytes subsets. Several correlates were also found between the cognitive assessments and physiological outcomes at baseline and 12 months follow-up. The results show that a high-quality, concentrated dietary supplement may offer an alternative option for persons with AD. The APMC formula may not only facilitate cognitive improvement, but may also improve the inflammatory status and immune functioning profile as well, thereby enhancing host's recovery and improving overall quality of life.

## EFFECTS OF ALOE SUPPLEMENTATION ON SKIN PHOTO-AGING

Collagen is the most abundant protein in our bodies, disturbing throughout in skin, bones, muscles, and organs, just about everywhere in the body. It provides skin's elasticity and also replaces dead skin cells. With aging, our bodies produce less collagen, which is one of the reasons why the elderly have sagging and wrinkled skin. Aloe vera gel can lessen the unavoidable problem because it stimulates collagen production in the skin. The increased collagen produced by aloe vera gel can significantly improve the skin's elasticity, and thereby remove and reverse wrinkles of the old appearance<sup>[5]</sup>. Aloe vera gel was shown to help rebuilding the skin collagen more quickly and can even prevent collagen breaking down through regeneration of the skin fibroblasts.

Chithra *et al*<sup>[44]</sup> reported the influence of aloe vera on the collagen content and its characteristics in healing dermal wounds. *Aloe vera* increased the collagen content of the granulation tissue as well as its degree of crosslinking as seen by increased aldehyde content and decreased acid solubility. Tanaka *et al*<sup>[45]</sup> confirmed that daily oral aloe sterol-containing aloe vera gel powder significantly reduced facial wrinkles in women aged  $\geq 40$  years, and aloe-sterol stimulated collagen and hyaluronic acid production by human dermal fibroblasts. The question on whether aloe sterol intake affected skin conditions following sunlight exposure was investigated by Tanaka

*et al*<sup>[46]</sup> with Japanese healthy 48 men, aged 30-59 years. The subjects were instructed to expose the measurement position of the arms to the sunlight outdoors every day for 12 weeks. The skin parameters were measured at 0 (baseline), 4, 8, and 12 weeks. Depending on the time for the revelation of the sunlight, the b\* value and melanin index increased and the skin moisture decreased. After taking an aloe sterol tablet daily for 12 weeks, the skin elasticity index levels were significantly higher than the baseline value. Aloe sterol ingestion increased skin elasticity in the photo-damaged skin of men aged  $<46$  years. Furthermore, the same research group evaluated the effects of oral aloe sterol supplementation on skin elasticity, hydration, and the collagen score in 64 healthy Japanese women aged 30-59 years. It was concluded that continued aloe sterol ingestion contributes to maintain healthy skin and prevents the skin photo-aging<sup>[47]</sup>. Saito *et al*<sup>[48]</sup> investigated the effects of oral aloe vera gel powder (AVGP) containing aloe sterols on skin elasticity and the extracellular matrix in UVB-irradiated hairless mice. The results suggested that AVGP has the ability to prevent the skin photo-aging. Furthermore, Misawa *et al*<sup>[49]</sup> investigated the protective effects of aloe sterols without polysaccharides, against UVB-induced skin photo-aging in mice, using aloe vera gel extract obtained by supercritical fluid extraction. The results indicated aloe sterols can prevent skin photo-aging through the suppression of inflammation and proinflammatory matrix metalloproteinase activity.

## ROLE OF BUTYRATE AS AN EPIGENETIC MODIFIER

Alterations in the gut microbiota have been associated with age-related phenotypes, and proper maintenance of microbiota with epigenetic modifiers, like probiotics has shown to be effective in managing chronic disease progression. Histone acetylation which is one of the key epigenetic modification processes controlling gene expression is known to be involved in lifespan determination. There is substantial evidence that indicate the geroprotective potential of histone deacetylase (HDAC) inhibitors. Vaiserman *et al*<sup>[50]</sup> reported the effects of HDAC inhibitor, butyrate on the parameters of viability and lifespan of *Drosophila melanogaster*. The flies fed butyrate at concentration of 10 and 20 mM through both pre-adult and adult stages demonstrated significant increases in mean lifespan in both males and females compared with controls. However, treatment with 20 and 40 mM butyrate during the adult stage only resulted in a statistically significant increase in male lifespan. Since butyrate is a known inducer of epigenetic changes, it raises the possibility of its use as a life-extending agent. These authors<sup>[51]</sup> proposed HDAC inhibitor as a promising therapeutics potential that is able to combat aging and its manifestations.

Becker *et al*<sup>[52]</sup> demonstrated that treatment of whole living *D. melanogaster* heads with HDAC/KDAC inhibitors, butyrate, and trichostatin A (TSA), induces a rapid transient increase of oxygen consumption rate. The authors suggested that these HDAC/KDAC inhibitors induce enhanced mitochondrial activity in a rapid manner and may be beneficial to treat various maladies. Investigation on novel probiotic and symbiotic formulations by Westfall *et al*<sup>[53]</sup> showed the extended longevity in male *D. melanogaster* through mechanisms of gut-brain-axis communication with implications in chronic disease management. Both the probiotic and symbiotic formulations restored markers of metabolic stress by modulating insulin resistance and energy regulatory pathways. The concomitant action of the gut microbiota on the key risk factors of aging makes it a powerful therapeutic tool against neurodegeneration, diabetes,

obesity, cardiovascular disease and other age-related chronic diseases. Storelli *et al.*<sup>[54]</sup> demonstrated that *Drosophila* microbiota promotes larval growth upon nutrient scarcity, and revealed that *Lactobacillus plantarum*, a commensal bacterium of the *Drosophila* intestine, is sufficient on its own to recapitulate the natural microbiota growth-promoting effect. The authors showed that *L. plantarum* exerts its beneficial effect on larval growth through the host nutrient sensing system. The study of Clark *et al.*<sup>[55]</sup> indicated a distinct shift in microbiota composition following intestinal barrier dysfunction, leading to systemic immune activation and organismal death in *D. melanogaster*. Alterations in microbiota dynamics could contribute to and also predict varying rates of health decline during aging.

The heat shock proteins (Hsps) also play a positive role in lifespan determination, and histone acetylation has been shown to be involved in transcription of Hsp genes in *Drosophila*. Zhao *et al.*<sup>[56]</sup> investigated the roles of HDAC in expression of Hsp genes during aging, and longevity determination in *D. melanogaster*. The results showed that the increase in acetylation level of histone H3 enhances the basal and inducible expression of Hsp 22 and Hsp 70 during aging, and extends both mean and maximum lifespan, to variable extents, in different lines of *D. melanogaster*. Moreover, the authors revealed the influences of histone acetylation modification on longevity and Hsp gene expression by using HDAC inhibitors, TSA and butyrate in *Drosophila*. These HDAC inhibitors caused the hyperacetylation of core histone H3, implicating the involvement of chromatin modulation in Hsp gene transcription. These data suggested a close correlation among histone acetylation, Hsp gene expression and longevity in *D. melanogaster*. Furthermore, the authors<sup>[57]</sup> showed that HDAC inhibitors caused the hyperacetylation of core histone H3, implicating the involvement of chromatin modulation in Hsp gene transcription. Greer *et al.*<sup>[58]</sup> found that HDAC inhibitor-mediated repression requires Hsp 90 activity. HDAC inhibitors promote the association of RNA polymerase II and negative elongation factor, a complex stabilized by Hsp 90 activity, at the same genomic sites. The activity of Hsps can be regulated by HDACs, and HDAC inhibitors block transcription elongation. The authors demonstrated that HDACs positively regulate transcription through the elongation machinery. A number of HDAC inhibitors are used in clinical trials for anti-cancer therapy. Jafary<sup>[59]</sup> described that histone deacetylation, similar to the induction of Hsps, is an essential process in the cellular defense against stress.

## SUMMARY

In the previous paper, we discussed the health-promoting potential of the balanced gut microbiota and health maintenance with long-term intake of aloe vera gel<sup>[60]</sup>. In the present review, we described the influence of lifelong aloe vera ingestion with microbiota on anti-obesity, healthy aging and longevity. Further mechanistic insights into how the microbiota modulates metabolic disease certainly pave the way for identification of innovative metabolic-based diagnostics and/or probiotic-based therapeutics.

It seems clear that the gut microbiota that produces butyrate from aloe vera gel ingestion plays an important role for maintaining our body's homeostasis by suppressing gastrointestinal tract-derived diseases and improving our general health status,

## REFERENCE

1. Ikeno Y, Hubbard GB, Lee S, Yu BP, Herlihy JT. The influence of long-term aloe vera ingestion on age-related disease in male Fischer 344 rats *Phytother Res.* 2002; **16(8)**: 712-718. [PMID: 12458471]; [DOI: 10.1002/ptr.1022]

2. Chandrashekars KT, Shakarad MN. Aloe or resveratrol supplementation in larval diet delays adult aging in the fruit fly, *Drosophila melanogaster* *J. of Gerontol A Biol Sci Med Sci.* 2011; **66A**: 965-971, [PMID: 21719611]
3. Yagi A. Putative prophylaxes of aloe vera for age-related diseases *J. of GHR* 2015; **4(1)**: 1407-1424 [DOI: 10.6051/j.issn.2224-3992.2015.04.416]
4. Rahmani AH, Aldebasi YH, Srikar S, Khan AA, Aly SM. Aloe vera: potential candidate in health management via modulation of biological activities *Pharmacogn. Rev.* 2015; **9(18)**: 120-126. [PMID: 26392709]; [DOI: 10.4103/0973-7847.162118]
5. Cho S, Lee MJ, Lee DH, Won CH, Kim SM, Chung JH. Dietary aloe vera supplementation improves facial wrinkles and elasticity and it increases the type I procollagen gene expression in human skin in vivo *Ann Dermatol (Seoul)* 2009; **21**: 6-11. [PMID: 20548848]; [DOI: 10.5021/ad.2009.21.1.6]
6. Chiodelli G, Pellizzoni M, Ruzickova G, Lucini L. Effect of different aloe fractions on the growth of lactic acid bacteria *J. of Food Sci.* 2017; **82**: 219-224. [PMID: 27886374]; [DOI: 10.1111/1750-3841.13568]
7. Yagi A, Kabbash A, Al-Madboly LA. Short chain fatty acids from fermentation by endophytic bacteria in Aloe vera leaf rind and gel *J. of GHR* 2016; **5(4)**: 2122-2124. [DOI: 10.17554/j.issn.2224-3992.2016.05.658]
8. Fakhry S, Sorrentini I, Ricca E, De Felice M, Baccigalupi L. Characterization of spore forming *Bacillus* isolated from the human gastrointestinal tract *J. of App. Microb.* 2008; **105**: 2178-2186 [DOI: 10.1111/j.1365-2672.2008.03934.x]
9. Torres MS, Waters B, von Turkovich M, Taajes DJ, Soares DJ, Craighead JE, White JF. Do *Bacillus* endophytes and epiphytes of food plants colonize the human digestive tract? *Poster for Symbiosis Congress in Lisbon, Portugal.* 2015 July 12-18, [DOI: 10.13140/RG.2.1.3134.7685]
10. Sacan O, Akev N, Yanardag R. In vitro inhibitory effect of *Aloe vera* (L) Burm. f. leaf extracts on the activity of some enzymes and antioxidant activity *Indian J. of Biochem & Biophys.* 2017; **54**: 82-89
11. Lim BO, Seong NS, Choue RW, Kim JD, Lee HY, Kim SY, Yu BP, Jeon TI, Park DK. Efficacy of dietary aloe vera supplementation on hepatic cholesterol and oxidative status in aged rats. *J Nutr Sci Vitaminol (Tokyo)* 2003; **49**: 292-296 [PMID: 14598919]
12. Bala S, Chugh NA, Bansal SC, Garg ML, Koul A. Protective role of *Aloe vera* against X-ray induced testicular dysfunction *Andrologia* 2017; **49(7)**: e12697. [PMID:27620003]; [DOI:10.1111/and.12697]
13. Behmanesh MA, Najafzadehvarzi H, Poormoosavi SM. Protective effect of *Aloe vera* extract against bisphenol A induced testicular toxicity in Wistar rats *Cell J.* 2018; **20(2)**: 278-283. [PMID:29633606];[DOI: 10.22074/cellj.2018.5256]
14. Kim K, Chung MH, Park S, Cha J, Baek JH, Lee SY, Choi SY. ER stress attenuation by aloe-derived polysaccharides in the protection of pancreatic  $\beta$ -cells from free fatty acid-induced lipotoxicity *Biochem Biophys Res Commun.* 2018; **500(3)**: 797-803 [PMID: 29684344]; [DOI: 10.1016/bbrc.2018.04.162]
15. Agarwal OP. Prevention of atheromatous heart disease *Angiology* 1985; **36**: 485-492
16. Dana N, Javanmard SH, Asgary S, Asnaashari H, Abdian N. The effect of aloe vera leaf gel on fatty streak formation in hypercholesterolemic rabbits *J Res Med Sci.* 2012; **17(5)**: 439-442. [PMID: 23626607]
17. Zheng GH, Yang L, Chen HY, Chu JF, Mei L. *Aloe vera* for prevention and treatment of infusion phlebitis *Cochrane Database Syst Rev.* 2014; **4 (6)**: CD009162 [PMID: 24895299]; [DOI: 10.1002/14651858.CD009162.pub2]
18. Gao Y, Jiang T, Mei S, Zhang S, Zhu C, Sun Y. Meta-analysis of *Aloe vera* for the prevention and treatment of chemotherapy-

- induced phlebitis *Int J Clin Exp Med* 2016; **9(6)**: 9642-9650 [ISSN: 1940-5901/IJCEM0023233]
19. Yu BP. Cellular defense against damage from reactive oxygen species *Physiological Review* 1994; **74**: 133-162
  20. Mathur U, Gahlout MS, Nisha, Bhan V. Analysis of anti-oxidant and anti-ageing properties of aloe vera gel on life history parameters of *Drosophila melanogaster* *Int J. of Adv Res in Sci and Eng* 2015; **4**: special issue (01): 227.
  21. Redman LM, Smith SR, Burton JH, Martin CK, Il'Yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging *Cell Metab* 2018; **27(4)**: 805-815.e4. [PMID: 29576535]; [DOI: 10.1016/j.cmet.2018.02.019]
  22. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance *Am J Physiol Endocrinol Metab.* 2018; **314(4)**: E396-E405. [PMID: 29351490]; [DOI: 10.1152/ajpendo.00261.2017]
  23. Das SK, Roberts SB, Bhapkar MV, Villareal DT, Fontana L, Martin CK, Racette SB, Fuss PJ, Kraus WE, Wong WW, Saltzman E, Piper CF, Fielding RA, Schwartz AV, Ravussin E, Redman LM. Body-composition changes in the comprehensive assessment of long-term effects of reducing intake of energy (CALERIE)-2 study: a 2-randomized controlled trial of calorie restriction in nonobese humans. *Am. J. Clin Nutr.* 2017; **105(4)**: 913-927. [PMID: 28228420]; [DOI: 10.3945/ajcn.116.137232]
  24. Obata F, Fons CO, Gould AP. Early-life exposure to low-dose oxidants can increase longevity via microbiome remodeling in *Drosophila* *Nature communications* 2018; **9**: 976 [DOI: 10.1038/s41467-018-03070-w]
  25. Tasi YT, Cheng PC, Pan TM. Anti-obesity effects of gut microbiota are associated with lactic acid bacteria *Appl Microbiol Biotechnol.* 2014; **98(1)**: 1-10 [PMID: 24232731]; [DOI: 10.1007/s00253-013-53446-3]
  26. Al-Madboly L, Kabbash A, El-Aasr M, Yagi A. Symbiotic effect of Aloe vera juice on the growth of *Lactobacillus fermentum* and *L.helveticus* isolate in vitro. *J. of GHR* 2017; **6(3)**: 2365-2369
  27. Mollica MP, Mattace Raso G, Cavaliere G, Trinchese G, De Filippo C, Aceto S, Prisco M, Pirozzi C, Di Guida F, Lama A, Crispino M, Tronino D, Di Vaio P, Berni Canani R, Calignano A, Meli R. Butyrate. Butyrate regulates liver mitochondrial function, efficacy, and dynamics in inulin-resistant obese mice *Diabetes* 2017; **66(5)**: 1405-1418. [PMID: 28223285]; [DOI: 10.2337/db16-0924]
  28. Jia Y, Hong J, Li H, Hu Y, Jia L, Cai D, Zhao R. Butyrate stimulates adipose lipolysis and mitochondrial oxidative phosphorylation through histone hyper-acetylation-associated  $\beta_3$ -adrenergic receptor activation in high-fat diet-induced obese mice *Exp Physiol.* 2017; **102(2)**: 273-281 [DOI: 10.1113/EP086114]
  29. Aquilar EC, da Silva JF, Navia-Pelaez JM, Leonel AJ, Lopes LG, Menezes-Garcia Z, Ferreira AVM, Capettini L des SA, Teixeira LG, Lemos VS, Alvarez-Leite S. Sodium butyrate modulates adipocyte expansion, adipogenesis, and insulin receptor signaling by upregulation of PPAR- $\gamma$  in obese Apo E knockout mice *J. Nutrition* 2018; **47**: 75-82 [DOI: 10.1016/j.nut.2017.10.007]
  30. Berni Canani R, 2018, Clinical Study Identifier: NCT02721953
  31. Goswami C, Iwasaki Y, Yada T. Short-chain fatty acids suppress food intake by activating vagal afferent neurons *The J. of Nutritional Biochemistry* 2018; **57**: 130-135 [DOI: 10.1016/j.jnutblo.2018; 03: 009]
  32. Whitt J, Woo V, Lee P, Moncivaiz J, Haberman Y, Denson L, Tso P, Alenghat T. Disruption of epithelial HDAC3 in intestine prevents diet-induced obesity in mice *Gastroenterology* 2018; pii: S0016-5083(18)30478-5 [PMID: 29689264]; [DOI: org./10.1053/j.gastro.2018.04.017]
  33. Rastelli M, Knauf C, Cani PD. Gut microbes and health: A focus on the mechanisms linking microbes, obesity, and related disorders *Obesity* (Silver Spring). 2018; **26(5)**: 792-800 [PMID: 29687645]; [DOI: 10.1002/oby.22175]
  34. Subash-Babu P, Alshatwi AA. Aloe-emodin inhibits adipocyte differentiation and maturation during in vitro human mesenchymal stem cell adipogenesis *J. Biochem & Molecular Toxicology* 2012; **26(8)**: 291-300 [DOI: 10.1002/jbt.21415]
  35. Sangeetha KN, Sujatha S, Muthusamy VS, Anand S, Shilpa K, Kumari PJ, Sarathkumar B, Thiyagarajan G, Lakshmi BS. Current trends in small molecule discovery targeting key cellular signaling events towards the combined management of diabetes and obesity *Bioinformatics* 2017; **13(12)**: 394-399 [PMID: 29379255]; [DOI: 10.6026/97320630013394]
  36. Alshatwi AA, Subash-Babu P. Aloe-emodin protects RIN-5F (Pancreatic  $\beta$ -cell) cell from glucotoxicity via regulation of pro-inflammatory cytokine and downregulation of Bax and caspase 3 *Biomol Ther.* 2016; **24(1)**: 49-56 [DOI: 10.4062/biomolther.2015.056]
  37. Youn DH, Kang JW, Jung Y, Park J, Kim HL, Jeong MY, Um JY, Kee JY, Hong SH. Barbaloin, a compound derived from *Aloe vera*, inhibits adipogenesis in 3T3-L1 adipocytes via AMPK- $\alpha$  activation *J of Obesity and Chronic Diseases* 2016; **1**: supplement 1 [DOI: 10.17756/jocd.2016-suppl1]
  38. Ji H, Liu Y, He F, An R, Du Z. LC-MS based urinary metabolomics study of the intervention effect of aloe-emodin on hyperlipidemia rats. *J of Pharmaceutical and Biomedical Analysis* 2018; **156(15)**: 104-115 [DOI: 10.1016/j.jpba.2018.04.015]
  39. Anand S, Muthusamy VS, Sujatha S, Sangeetha KN, Bharathi RR, Sudhagar S, Poornima DN, Lakshmi BS. Aloe-emodin glycoside stimulates glucose transport and glycogen storage through PI3K dependent mechanism in L6 myotubes and inhibits adipocyte differentiation in 3T3L1 adipocytes *FEBS Lett.* 2010; **584(14)**: 3170-3178 [PMID: 20541550]; [DOI: 10.1016/j.febslet.2010.06.004]
  40. Ronan L, Alexander-Bloch A, Wagstyl K, Farooqi S, Bryane C, Tyler LK, Cam-CAN, Fletcher PC. Obesity associated with increased brain age from midlife *Neurobiology of Aging* 2016; **47**: 63-70 [DOI: 10.1016/j.neurobiolaging.2016.07.010]
  41. Abdollahnejad F, Mosaddegh M, Nasoohi S, Mirnajafi-Zadeh J, Kamalinejad M, Faizi M. Study of sedative-hypnotic effects of Aloe vera L aqueous extract through behavioral evaluations and EEG recording in rats *Iran J. Pharm Res.* 2016; **15(1)**: 293-300 [PMID: 27610170]
  42. Halder S, Mehta AK, Mediratta PK. *Aloe vera* improves memory and reduces depression in mice *Nutritional Neuroscience* 2013; **16**: 250-254 [PMID: 23394255]; [DOI: 10.1179/1476830512Y.0000000050]
  43. Lewis JF, McDaniel HR, Agronin ME, Loewenstein DA, Riveros J, Meatre R, Martinez M, Colina N, Abreu D, Konefal J. Efficiency of an aloe polymannose multinutrient complex on cognitive and immune functioning in Alzheimer's disease. *J Alzheimer Disease* 2013; **33**: 393-406 [PMID: 229760773]; [DOI: 103233/JAD-2012-121381]
  44. Chithra P, Sajithlal GB, Chandrakasan G. Influence of *Aloe vera* on collagen characteristics in healing dermal wounds in rats *Mol Cell Biochem.* 1998; **181(1-2)**: 71-76. [PMID: 9562243]
  45. Tanaka M, Misawa E, Yamauchi K, Abe F, Ishizaki C. Effects of plant sterols derived from aloe vera gel on human dermal fibroblasts in vitro and on skin condition in Japanese women *Clin Cosmet Investig Dermatol.* 2015; **8**: 95-104 [PMID: 25759593]; [DOI: 10.2147/CCID.S75441]
  46. Tanaka M, Yamamoto Y, Misawa E, Nabeshima K, Saito M, Yamauchi K, Abe F, Furukawa F. Aloe sterol supplementation improves skin elasticity in Japanese men with sunlight-exposed skin: a 12-week double-blind, randomized controlled trial *Clin Cosmet Investig Dermatol.* 2016; **9**: 435-442, [PMID: 27877061]; [DOI: 10.2147/CCID.S118947]

47. Tanaka M, Yamamoto Y, Misawa E, Nabeshima K, Saito M, Yamauchi K, Abe F, Furukawa F. Effects of aloe sterol supplementation on skin elasticity, hydration, and collagen score: A 12-week double-blind, randomized, controlled trial *Skin Pharmacology and Physiology* 2016; **29**: 309-317 [PMID: 28088806]; [DOI: 10.1159/000454718]
48. Saito M, Tanaka M, Misawa E, Yao R, Nabeshima K, Yamauchi K, Abe F, Yamamoto Y, Furukawa F. Oral administration of aloe vera gel powder prevents UVB-induced decrease in skin elasticity via suppression of overexpression of MMPs in hairless mice. *Biosci Biotechnol Biochem.* 2016; **8(7)**: 1416-1424. [PMID: 27045316]; [DOI: 10.1080/09168451.2016.1156480]
49. Misawa E, Tanaka M, Saito M, Nabeshima K, Yao R, Yamauchi K, Abe F, Yamamoto Y, Furukawa F. Protective effects of aloe sterols against UVB-induced photo-aging in hairless mice *Photodermatol. Photoimmunol. Photomed.* 2017; **33(2)**: 101-111 [PMID: 27995657]; [DOI: 10.1111/phpp.12286]
50. Vaiserman AM, Koliada AK, Koshel NM, Simonenko AV, Pasiukova EG. Effect of the histone deacetylase inhibitor sodium butyrate on the viability and life span in *Drosophila melanogaster* *Adv Gerontol.* 2012; **25(1)**: 126-131. [PMID: 22708457]
51. Pasyukova EG, Vaiserman AM. HDCA inhibitors: A new promising drug class in anti-aging research *Mechanism of Ageing and Development* 2017; **166**: 6-15 [DOI: 10.1016/j.mad.2017.08.008]
52. Becker L, Schmitt Nogueira M, Klima C, Hrabe de Angelis M, Peleg S. Rapid and transient oxygen consumption increase following acute HDAC/KDAC inhibition in *Drosophila* tissue *Scientific Reports* 2018; **8**: 4199 [DOI: 10.1038/s41598-018-22674-2]
53. Westfall S, Lomis N, Prakash S. Longevity extension in *Drosophila* through gut-brain communication *Scientific Reports* 2018; **8**: 8362 [DOI: 10.1038/s41598-018-25382-z]
54. Storelli G, Defaye A, Erkosar B, Hols P, Royet J, Lelier F. *Lactobacillus plantarum* promotes *Drosophila* systemic growth by modulating hormonal signals through TOR-dependent nutrient sensing *Cell Metabolism* 2011; **14**: 403-414 [DOI: 10.1016/j.cmet.2011.07.012]
55. Clark RI, Salazar A, Yamada R, Fitz-Gibbon S, Morselli M, Alcaraz J, Rana A, Rera M, Pellegrini M, Ja WW, Walker DW. Distinct shifts in microbiota composition during *Drosophila* aging impair intestinal function and drive mortality *Cell Reports* 2015; **12**: 1656-1667. [PMID: 26321641]; [DOI: 10.1016/j.celrep.2015.08.004]
56. Zhao YM, Sun H, Lu J, Li XX, Chen X, Tao D, Huang W, Huang BQ. Lifespan extension and elevated hsp gene expression in *Drosophila* caused by histone deacetylase inhibitors *J Exp Biol.* 2005; **208(Pt 4)**: 697-705 [PMID: 15695762]; [DOI: 10.1242/jeb.01439]
57. Zhao YM, Chen X, Sun H, Yuan ZG, Ren GL, Li XX, Lu J, Huang BQ. Effects of histone deacetylase inhibitors on transcriptional regulation of the hsp70 gene in *Drosophila* *Cell Res.* 2006; **16(6)**: 566-576. [PMID: 16775628]; [DOI: 10.1038/sj.cr.7310074]
58. Greer CB, Tanaka Y, Kim YJ, Xie P, Zhang MQ, Park IH, Kim TH. Histone deacetylases positively regulate transcription through the elongation machinery *Cell Rep.* 2015; **13(7)**: 1444-1455 [PMID: 26549458]; [DOI: 10.1016/j.celrep.2015.10.013]
59. Jafary H. HDAC inhibitors and Heat shock proteins (Hsps) *Biomacromol. J.* 2017; **3(1)**: 5-17,
60. Yagi A, Yu BP. Gut microbiota: Influence of aloe vera gel and calorie restriction *J. of GHR.* 2017; **6(3)**: 2349-2353 [DOI: 10.17554/j.issn.2224-3992.2017.06.669]