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REVIEW

## Prophylactic Role of Aloe Components, Butyrate Fermented, Micrnas, and Hyaluronan on Alzheimer's Disease, Parkinson's Disease, and Osteoarthritis in Knee Joints: Case Reports Of Aloe Vera Juice Ingestion Producing Intestinal Butyrogenic Microbiome and Bone Regeneration

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### ABSTRACT

Host microbial cross talk is essential to maintain intestinal homeostasis. However, maladaptation of the response through microbial dysbiosis or defective host defense toward invasive intestinal microbial results in chronic inflammation and the mild cognitive impairment. The role of active constituents from Aloe

species, fermented butyrate, and micRNAs on Alzheimer's disease, and Parkinson's disease is discussed on the basis of gut microbiota-gut-brain axis. And prophylactic hyaluronan to knee osteoarthritis is discussed on the basis of functional relationship between osteogenesis and angiogenesis in tissue regeneration. Furthermore, two case reports suggest that the successive ingestion of aloe vera juice provides high concentration of the butyrogenic microbiome *Faecalibacterium* spp. in fecal, and could play a beneficial role for tissue repair and bone regeneration.

**Key words:** Aloe active constituents; Butyrogenic microbiome; Alzheimer's disease; Parkinson's disease; Osteoarthritis; Case reports

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### INTRODUCTION

Aloe species have antioxidant and anti-inflammatory properties that can help protect brain health. Aloe extracts reduced the potential of the cells to be oxidized and lowered the formation of harmful reactive oxygen species in the presence of Amyloid  $\beta$ . The extracts also protected mitochondrial functions (mitochondria energy producing units in the cell) and also improved cell survival. Aloe vera contains active compounds that are natural  $\beta$ -secretase ( $\beta$ -side amyloid precursor protein-cleaving enzyme: BACE) inhibitors and can aid in the inhibition of  $\beta$ -secretase enzyme and thus prevent dementia. The  $\beta$ -secretase is one of the enzymes that contribute to the formation of Amyloid  $\beta$  plaques which lead to dementia, thus its inhibition can protect brain health and prevent Alzheimer's disease (AD).

Aging in human is associated with a reduction in the beneficial commensal microbes, which control expansion of pathogenic commensals and maintain the integrity of the intestinal barrier through the production of mucus and lipid metabolisms, such as short chain fatty acids (SCFAs); butyric acid. Alterations in gut microbiota might be accompanied by altered concentrations of SCFAs. Thus, interventions that alter the composition of the gut microbiota might reduce pro-inflammatory state and rejuvenate immune functions to provide anticancer and insulin secretion benefits in frail elderly people<sup>[1]</sup>.

Since Amyloid  $\beta$  ( $A\beta$ ) aggregation is hypothesized to be the most crucial step of the pathogenic process of AD, the strategy to inhibit  $A\beta$  aggregation has emerged as a promising approach to treat AD.  $A\beta$  is one of the hallmarks for AD, and generated from  $A\beta$  protein precursor processing by  $\beta$ - and  $\gamma$ -secretases through the amyloid cascade pathway.  $A\beta$  normally has a propensity for self-aggregation, resulting in  $A\beta$  fibril formation which ultimately forms senile plaques extracellularly, causing neuronal damage and synaptic dysfunction.  $A\beta_{40}$  is the common, more soluble form of  $A\beta$ .  $A\beta_{42}$  has two extra amino acids on the end of the peptide. The toxicity of  $A\beta_{42}$  is much greater than  $A\beta_{40}$ .

Several miRNAs participate in signaling networks through the intervention of gut microbiota. The crosstalk between the gut microbiota and physical organs and how the gut microbiota and miRNAs regulate each other while influencing the host via genes, proteins or metabolites were discussed. The importance of butyrate, a HDAC inhibitor, and host-miRNA-microbiota interaction in regulation of Alzheimer's disease and Parkinson's disease have been demonstrated.

Present review is focused on aloe components, butyrate fermented, micRNAs and hyaluronan to alleviate Alzheimer's disease, Parkinson's disease, and tissue repair and bone regeneration. Furthermore two case reports show that an old frail person through the increase in butyrogenic microbiome and a 40-years old-nurse who had Chiari malformation syringomyelia recovered well QOL with aloe vera juice successive ingestion.

## ACTIVE CONSTITUENTS FROM ALOE ARBORESCENS, A. VERA AND A. NOBILIS AS BACE INHIBITORS

Beta-site amyloid precursor protein Cleaving Enzyme 1 ( $BACE_1$ ) has been one of the prime therapeutic targets for Alzheimer's disease. Gao *et al*<sup>[2]</sup> aimed to seek for new compounds as BACE inhibitors from *A. arborescens*. Among eight compounds aloenin A, chromone derivatives and barbaloin showed moderate inhibitory activity on BACE.

### BACE<sub>1</sub> (beta-Secretase) inhibitor from *A. vera* and *A. nobilis*

Liang *et al*<sup>[3]</sup> investigated four new chromone glycosides and among them aloeresin D and C-2'-decoumaroyl-aloesin G showed significant inhibitory activity against  $BACE_1$  with  $IC_{50}$  value of 39.0 and 20.5  $\mu$ M, as well as inhibition of  $A\beta_{42}$  production by 7.4 and 12.3 %, respectively, in B103 neuroblastoma cells at 30 ppm.

### Aloe arborescens extract as agents for the management of Alzheimer's disease

Clementi *et al*<sup>[4]</sup> provided evidence that *A. arborescens* extract protect IMR32, a neuroblastoma human cellular line, from pretreatment with *A. arborescens* maintains an elevate cell viability and exerts a protective effect on mitochondrial functionality, as evidenced by oxygen consumption experiments. The protective mechanism exerted by *A. arborescens* seems to be related to lowering of oxidative potential

of the cells, as demonstrated by the ROS measurement compared with the results obtained in the presence of  $A\beta_{1-42}$  peptide alone. The authors suggested use of *A. arborescens* extract could be developed as agents for the management of Alzheimer's disease.

### Efficacy of aloe polymannose multi-nutrient complex on cognitive and immune functioning in Alzheimer's disease

Lewis *et al*<sup>[5]</sup> demonstrated that high dose consumption of aloe polysaccharide (Acemannan) for 9-12 months improved cognitive function in Alzheimer's disease (AD). The authors showed improvements in both clinical and physiological outcomes for a disease that otherwise has no standard ameliorative remedy. Dietary fibers acemannan were metabolized by gastrointestinal bacteria into short chain fatty acids.

## MODIFIED MEDITERRANEAN-KETOGENIC DIET MODULATES GUT MICROBIOME AND SHORT-CHAIN FATTY ACIDS IN ASSOCIATION WITH ALZHEIMER'S DISEASE MARKERS IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT

Nagpal *et al*<sup>[6]</sup> examined how the gut microbiome differs in older adults with mild cognitive impairment compared to cognitive normal counterparts, and whether and how a modified Mediterranean-ketogenic diet (MMKD) alters the gut microbiome signature in association with cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers. At baseline, subjects with normal vs. impaired cognition show no notable difference in microbiome diversity but several unique microbial signatures are detected in subjects with mild cognitive impairment. *Proteobacteria* correlate positively with  $A\beta_{42}:A\beta_{40}$  while fecal propionate and butyrate correlates negatively with  $A\beta_{42}$  in subjects with mild cognitive impairment. The data suggested that specific gut microbial signatures may depict the mild cognitive impairment and that the MMKD can modulate the gut microbiome and metabolites in association with improved AD biomarkers in CSF.

## EFFECT OF THE HDAC INHIBITOR SODIUM BUTYRATE ON THE VIABILITY AND LIFESPAN IN DROSOPHILA MELANOGASTER

Vaiserman *et al*<sup>[7]</sup> showed that the dietary supplementation with histone deacetylase inhibitor butyrate throughout adult stage or both pre-adult and adult stages results in increase of life span in *Drosophila melanogaster*. It was suggested that because of the impact of sodium butyrate on epigenetic control of gene function and therefore possibility of long-term effects, sodium butyrate supplementation during the larval stage of development only may also increase adult life span. The authors<sup>[8]</sup> furthermore carried out to verify the assumption. The nutritional supplementation with sodium butyrate during the larval stage at the concentration of 20 mmol/L resulted in a significant increase in the male mean life span; maximum life span was significantly increased in male treated with sodium butyrate at concentrations of 10, 20 and 40 mmol/L. Female mean life span unchanged following the sodium butyrate administration; maximum life span was significantly in female group treated with sodium butyrate at concentration of 10 mmol/L only. Female reproductive activity was the same in all groups. To test the

hypothesis that the observed long-term effect of sodium butyrate exposure on the flies' longevity could be caused by the induction of persistent epigenetic changes, the level of expression of longevity-associated gene (*hsp70*, *sir2* and *InR*) were determined. The expression level of *sir2* gene, known to mediate longevity in the fly through a pathway related to calorie restriction, in the group treated at the larval stage with 20 mmol/L sodium butyrate was significantly higher after the stress (starvation) than in the control group.

## THE ROLE OF PROBIOTICS IN PREVENTING ALZHEIMER'S DISEASE BY REGULATION GUT MICROBIOTA-GUT-BRAIN AXIS

Sun *et al*<sup>[9]</sup> examined the anti-neuro-inflammatory effect and its mechanism of probiotic *Clostridium butyricum* (CB) against Alzheimer's disease by regulating gut microbiota (GM)-gut-brain axis. CB treatment prevented cognitive impairment, A $\beta$  deposits, microglia activation, and production of TNF- $\alpha$  and interleukin-1 in the brain of APP/PS1 mice. Abnormal GM and butyrate are reversed after CB treatment. Notably butyrate treatment reduced the level of CD11b and COX-2, and suppressed phosphorylation of NF- $\kappa$ B p65 in the A $\beta$ -induced BV2 microglia. The findings indicated that CB treatment could attenuate microglia-mediated neuro-inflammation via regulating the GM-gut-brain axis, which is mediated by the metabolite butyrate.

### Sodium butyrate improves memory and modulates the activity of histone deacetylases in aged rats after the administration of D-galactose

Garcez *et al*<sup>[10]</sup> reported that sodium butyrate reversed habituation memory damage and aversive memory damage in the aged and/or in D-galactose-induced rats. Furthermore the authors investigated that sodium butyrate reduced HDACs activity increases caused by D-galactose and frequency and rate of DNA damage caused by D-galactose. The protective effects of sodium butyrate on the memory of naturally aged and D-galactose induced aging in rats were exhibited.

### The potential role of SCFAs in A $\beta$ mediated pathological processes that play key roles in Alzheimer's disease pathogenesis

Multiple complementary assays were used to investigate individual SCFAs for their dose-responsive effects in interfering with the assembly of A $\beta$ 1-40 and A $\beta$ 1-42 peptides into soluble neurotoxic A $\beta$  aggregates. Ho *et al*<sup>[11]</sup> found that several select SCFAs, propionic, valeric and butyric acids, are capable of potent inhibiting A $\beta$  aggregations, in vitro. Dietary fibers are metabolized by gastrointestinal bacteria into SCFAs and selected SCFAs potency interferes with A $\beta$  fibril formation.

### SCFAs or metabolites produced by bacteria affect blood-brain-barrier permeability

SCFAs are known to enhance the integrity of the intestinal epithelial barrier by facilitating the assembly of tight junctions. Braniste *et al*<sup>[12]</sup> evaluated blood-brain-barrier (BBB) permeability in germ-free adult mice monocolonized with a single bacterial strain, *Clostridium tyrobutyricum*, that produces mainly butyrate or with *Bacteroides thetaiotaomicron* which produces mainly acetate and propionate. Sodium butyrate-treated mice demonstrated decreased BBB permeability, compared to that in germ-free adult mice, that was equivalent to that of pathogen-free adult mice.

### Probiotic supplementation in patients with Alzheimer's dementia

Dysbiosis of intestinal microbiota in the elderly can cause a leaky gut, which may result in silent systemic inflammation and promote neuro-inflammation; A relevant patho-mechanism in the early course of Alzheimer's disease. Lehuber *et al*<sup>[13]</sup> investigated the rebalancing of the microbiome could beneficially impact on gut inflammation and immune activation. Twenty patients were supplemented with a multispecies probiotic cocktail for one month. The results demonstrated a significant increase in serum kynurenine and increases in fecal zonulin and *Faecalibacterium prausnitzii* concentration. (zonulin: a protein that modulates the permeability of tight junctions between cells of the wall of the digestive tracts.)

## SODIUM BUTYRATE PROTECTS N2A CELLS AGAINST TOXICITY IN VITRO AND IMPROVES COGNITIVE MEMORY PERFORMANCE IN AN ALZHEIMER'S DISEASE TRANSGENIC MOUSE MODEL AT AN EARLY DISEASE STAGE

Sun *et al*<sup>[14]</sup> aimed to research the protective effects of sodium butyrate (NaB) on neurons against A $\beta$  toxicity and to uncover the underlying mechanisms. The results showed that 2 mmol NaB had a significant improvement effect on A $\beta$ -induced mouse neuroblastoma (N2a) cell injury, by increasing cell viability and reducing ROS to reduce injury. In addition, by acting on the GPR109A receptor, NaB regulates the expression of Alzheimer's disease (AD)-related genes such as APP, NEP, and BDNF. Therefore NaB protects N2a cells from A $\beta$ -induced cell damage through activating GPR109A, which provides an innovative idea for the treatment of AD.

Fernando *et al*<sup>[15]</sup> investigated the ability of the HDAC inhibitor sodium butyrate (NaB) to attenuate memory deficits in the 5xFDA mouse model of AD following a 12-week feeding regimen. 5xFDA mice demonstrated a unique time course of A $\beta$ -pathology, developing A $\beta$ -plaques as early as 2 months. Male mice were assigned to either a control diet or a NaB-supplemented diet which was administered at either of 5mg/kg/day or 15mg/kg/day for 12 weeks (each group, N=15). NaB had profound effects on A $\beta$  levels and on associative learning and cognitive functioning. A 40% reduction in brain A $\beta$  levels and a 25% increase in fear response in both the cued and contextual testing was observed in the NaB-treated animals compared to the control group.

## A CORRELATION BETWEEN GUT DYSBIOSIS AND AMYLOID PATHOLOGY IN ALZHEIMER'S DISEASE

Marizzoni *et al*<sup>[16]</sup> investigated the association between amyloid pathology, bacterial products such as lipopolysaccharide (LPS) and short chain fatty acids (SCFAs: acetate, valerate, butyrate), inflammatory mediators, and markers of endothelial dysfunction in Alzheimer's disease (AD). The authors reported a novel association between gut microbiota-related products and systemic inflammation with brain amyloidosis via endothelial dysfunction, suggesting that SCFAs and LPS represent candidate pathophysiologic links between the gut microbiota and AD pathology. This discovery paves the way for potential highly innovative protective strategies: through the administration of bacterial cocktail or of prebiotics to feed the good bacteria in our intestine.

## THE EMERGING ROLE OF MICRORNAS IN ALZHEIMER'S DISEASE

Femminella *et al*<sup>[17]</sup> reviewed the emerging role of microRNAs in Alzheimer's disease. MicroRNAs (miRNAs) are a novel class of small (18-25 nucleotides), single-stranded non-coding RNAs involved in the post-transcriptional regulation of gene expression. MiRNAs are involved in almost all biological processes, such as proliferation, development, apoptosis, inflammation and their expression is highly regulated, either by enzymes which stabilize mature miRNAs or epigenetic mechanisms such as DNA methylation or histone modifications. MiRNAs undergo a specific tissutal and temporal distribution, as indicated by several studies on miRNA profiling in different chronic diseases and they have been found in all human bio-fluids. In particular, these small RNAs have demonstrated being stable in cerebrospinal fluid and blood, probably thanks to the fact that they can be transported by liposomes or lipoproteins which prevent them from degradation.

### The roles of miRNAs in the central nervous system of Alzheimer's disease

It has been demonstrated that specific miRNAs are expressed in the central nervous system (CNS), where they regulate neuronal differentiation, synaptic plasticity and neural outgrowth. Wang *et al*<sup>[18]</sup> investigated the patterns of micRNA expression. MicRNA (miRNA) expression was assessed in human cerebral cortical gray matter (GM) and white matter (WM) in order to provide the first insights into the difference between GM and WM miRNA repertoires across a range of AD pathology. Patterns of miRNA expression in cortical GM may contribute to AD pathogenetically, because the aggregate change in miRNA expression observed early in the disease would be predicted to cause profound changes in gene expression.

### MiR-31 is a transcriptional target of histone deacetylase inhibitors and a regulator of cellular senescence

Histone deacetylase inhibitor inhibits expression of polycomb group proteins and can differentially regulate expression of miRNAs. The micRNA-31 (miR-31) has been shown to be overexpressed in metastatic breast cancer. It promotes multiple oncogenic phenotypes, including proliferation, motility, and invasion of cancer cells. Cho *et al*<sup>[19]</sup> investigated that HDAC inhibitor up-regulated expression of miR-31, which down-regulated BMI1 and induced cellular senescence. MiR-31 is a novel target of HDAC inhibitor, and is a novel regulator of cellular senescence.

### MiR-31 improves cognitive and abolishes Amyloid- $\beta$ pathology by targeting amyloid precursor protein (APP) and BACE<sub>1</sub> in an animal model of Alzheimer's disease

Barros-Viegas *et al*<sup>[20]</sup> identified several miRNAs capable of targeting key proteins of the amyloidogenic pathway. The expression of one of these miRNAs, miR-31 found to be decreased in AD patients, was able to simultaneously reduce the level of APP and BACE<sub>1</sub> mRNA in the hippocampus of 17-month-old AD triple-transgenic (3xTg-AD) female mice, leading to a significant improvement of memory deficits and a reduction in anxiety and cognitive inflexibility. The authors suggested that miR-31-mediated modulation of APP and BACE<sub>1</sub> can become a therapeutic option in the treatment of AD.

### MiR-124 acts as a target for Alzheimer's disease by regulating BACE<sub>1</sub>

An *et al*<sup>[21]</sup> identified that miR-124 levels are gradually decreased in

AD and demonstrated that miR-124 suppresses BACE<sub>1</sub> expression by directly targeting the 3'UTR of Bace1 mRNA in vitro. Inhibition of miR-124 significantly increased BACE<sub>1</sub> levels in neuronal cells. In contrast, miR-124 overexpression significantly suppressed BACE<sub>1</sub> expression in cells. And finally the authors determined that downregulation of miR-124 alleviated A $\beta$ -induced viability inhibition and decreased apoptosis in SH-SY5 cells. The results demonstrated that miR-124 is a potent negative regulator of BACE<sub>1</sub> in the cellular AD phenotype and might be involved in the pathogenesis of AD.

## THE EFFECT OF ALOE VERA EXTRACT ON ACETYLCHOLINESTERASE AND MONOAMINE OXIDASE IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor impairments, as well as non-motor symptoms that include constipation, anxiety, depression, and sleep behavior disorder. Aloe vera extract as a dietary supplement for treatment of depression disease, such as Parkinson's disease was evaluated because it has an effect on inhibiting of enzymes monoamine oxidase (MAO) and acetylcholine esterase (AChE). Aloe vera extract showed a good enzyme inhibition with increased of the concentration for MAO (81.13%) and for AChE (89.82%) in 0.1M for aloe vera extract<sup>[22]</sup>.

$\alpha$ -Synuclein ( $\alpha$ -Syn) damage and its deposition cause neurodegeneration in the brain resulting in PD. The abnormal  $\alpha$ -Syn accumulation has been identified in the biopsies within colon and rectum of PD patients. Colonization of  $\alpha$ -Syn-overexpressing mice with microbiota from PD-affected patients enhances physical impairments compared in microbiota transplants from healthy human donors.  $\alpha$ -Syn is considered a major culprit in PD pathophysiology<sup>[23]</sup>.

## SHORT CHAIN FATTY ACIDS AND GUT MICROBIOTA DIFFER BETWEEN PATIENTS WITH PARKINSON'S DISEASE AND AGE-MATCHED CONTROL

Patients with Parkinson's disease (PD) have gastrointestinal symptoms (e.g. constipation) and exhibit the PD-typical pathohistology in the enteric nervous system (ENS). Both clinical symptoms and pathophysiological changes in the ENS occur at early stages and can precede the motor manifestations of PD. SCFAs concentrations and microbiota composition in fecal samples of 34 PD patients and 34 age-matched controls were quantitatively examined by Unger *et al*<sup>[24]</sup>. The fecal SCFAs concentration reduced in PD patients compared to controls. Phylum *Bacteroides* and family *Proteobacteria* were reduced and *Enterobacteriaceae* were more abundant in fecal samples from PD patients compared to matched controls. The results confirmed the reduction in fecal SCFAs concentrations, inducing alteration in the ENS and contributing to gastrointestinal dysmotility in PD.

### Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features

Li *et al*<sup>[25]</sup> compared the structure of gut microbiota in 24 Parkinson's disease (PD) patients and 14 healthy controls and explored correlations between gut microbiota and PD clinical features. The putative cellulose degrading bacteria from the genera *Blautia*,

*Faecalibacterium* and *Ruminococcus* were significantly decreased in PD compared to healthy controls. The results suggested that structural changes of gut microbiota in PD are characterized by the decreases of putative cellulose degraders and the increases of putative pathobionts, which may potentially reduce the production of SCFAs, and produce more endotoxins and neurotoxins; and these changes are potentially associated with the development of PD pathology.

A few studies using oral administration of sodium butyrate indicate beneficial effects in PD animal models; however prebiotic fibers that generate butyrate locally in the gut may be more effective. The design and selection of butyrogenic prebiotic fibers would allow preclinical studies to evaluate how gut-derived butyrate could affect PD pathophysiology. Cantu-Jungles *et al* [26] discussed potential benefits of increasing gut butyrate production in PD through a prebiotic approach.

## PLASMA SHORT-CHAIN FATTY ACIDS IN PATIENTS WITH PARKINSON'S DISEASE

Short-chain fatty acids (SCFAs) are exclusively produced by gut microbiota and are reduced in feces of patients with Parkinson's disease (PD). Shin *et al* [27] investigated a case-control study on peripheral concentration of SCFAs based on evidence of pathologic changes in the blood-brain barrier in PD and the possible role of SCFAs in blood-brain barrier permeability. Plasma SCFAs were paradoxically increased in PD and were associated with disease severity and antiparkinsonian medications.

## CIRCULATING INFLAMMATORY MIRNAS ASSOCIATED WITH PARKINSON'S DISEASE PATHOPHYSIOLOGY

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, being largely characterized by motor features and affecting 1-2% of people older than 65 years. MicroRNAs (miR) are small non-coding RNAs, whose degeneration has been associated with neurodegeneration in PD. Oliveira *et al* [28] selected miRNAs targeting cell death and/or inflammation pathways and compared their expression in the serum of PD patients and healthy controls. The authors found miR-146a, miR-335-3p, and miR-335-6p downregulated in idiopathic PD patients and the leucine-rich repeat kinase 2-PD patients versus controls in both cohorts. The authors identified a panel of inflammatory related miRNA differentially expressed between PD patients and healthy controls that highlight key pathophysiological processes and may contribute to improve disease diagnosis.

Ozdilek and Demircan [29] determined the serum expression levels of seven candidate miRNAs; miR-19a, miR-19b, miR-29a, miR-29c, miR-181, miR-195 and miR-221 in Turkish patients with Parkinson's disease (PD) and explored their potential role in the diagnosis of PD. The authors reported the study including 51 PD patients and 20 healthy controls. The authors exhibited that serum miR-29c expression level might be potential biomarker in the diagnosis on Turkish PD patients. Han *et al* [30] examined whether miRNA-29s (miR-29s) in serum are associated with cognitive impairment in PD. Thirty-nine PD patients with normal cognition, 37 PD patients with mild cognitive impairment, 22 PD patients with dementia and 40 healthy controls were recruited. Detailed clinical evaluations and a schedule of neuropsychological tests were administered to all patients. MiR-29s expression in serum samples was assessed using

reverse-transcription quantitative real-time PCR. The analysis of the cognitive domains found that the miR-29s levels were all associated with memory performance in PD patients. MiR-29s are associated with cognitive impairment in PD.

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

Hyaluronan (hyaluronic acid; HA) is a polysaccharide with multiple functions in the human body being involved in creating flexible and protective layers in tissue and many significant pathways during embryonic development, wound healing, inflammation and cancer. HA is an important component of active pharmaceutical ingredients for treatment of arthritis and osteoarthritis. Putri *et al* [31] found HA on aloe vera just below the waxy cuticle of rind, these is an area where aloe correlated bacteria live. Gram-positive microbes *Streptococci* which are able to produce HA through bacterial pathway were only found on the surface of Aloe vera, whereas *Coccobacillii* (*Staphylococcus morlillorium*, *Enterococcus faecium*, and other Gram-negative rods) are observed only in gel part. It was found out that the rind part of aloe vera have the highest potential of high content of HA.

## THE EFFICACY OF ORAL HYALURONIC ACID (HA) ADMINISTRATION FOR OSTEOARTHRITIS (OA) IN KNEE JOINTS

Tashiro *et al* [32] investigated sixty osteoarthritic subjects (Kellgren-Lawrence grade 2 or 3) were randomly assigned to the HA or placebo group. The subjects in the HA group were given 200mg of HA once a day every day for 12 months, while the subjects in the placebo group were given placebo. The subjects in both groups were required to conduct quadriceps strengthening exercise everyday as part of the treatment. The subject's symptoms were evaluated by the Japanese Knee Osteoarthritis Measure (JKOM) score. The symptoms of the subjects as determined by the JKOM score improved with time in both the HA and placebo groups. Oral administration of HA may improve the symptoms of knee OA in patients aged 70 years or younger when combined with the quadriceps strengthening exercise.

Huang *et al* [33] tested the hypothesis that HA can significantly promote the osteogenic potential of BMP-2/ACS ( human morphogenetic protein-2/absorbable collagen sponge), an efficacious product to heal large oral bone defects, thereby allowing its use at low dosages and, reducing its side-effects due to the un-physiologically-high doses of BMP-2. In conclusion an optimal combined administration of HA could significantly promote osteogenic and angiogenic activity of BMP-2/ACS, thus potentially minimizing its potential side-effects.

## Hyaluronic acid versus glucocorticoid injections for nonradicular pain in the lumbar spine

Fuchs *et al* [34] investigated the efficacy and safety of intraarticular sodium hyaluronate (SH) compared with intraarticular glucocorticoids (triamcinolone acetone, TA) in the treatment of chronic nonradicular lumbar pain. Intraarticular treatment of facet joint in 60 patients with chronic nonradicular pain in the lumbar spine resulted in a marked reduction in pain with improved function and better quality of life, which was at least equal to the effect of a course of TA injections.

**Several preparations of hyaluronic acid for many FDA approved indications**

Walker *et al*<sup>[35]</sup> published several preparations of hyaluronic acid (HA) being available for many United States Food and Drug Administration Labeled indications. The most common application indicators are for cosmetics, and for intraarticular uses. For instance; Intra-articular injection for pain relief in patients with mild to moderate osteoarthritis of the knees, Intradermal injection, Subcutaneous injection, Subperiosteal injection, Submucosal injection, Topical cream/gel Ophthalmics.

**EFFECT OF ALOE VERA GEL TO INTERVERTEBRAL DISK DEGENERATION IN RABBITS**

Disk degeneration is a common cause of low back pain. Busuyi *et al*<sup>[36]</sup> investigated the effect of aloe vera gel (AVG) on the histomorphometric changes in the intervertebral disk of annual-punctured rabbits. The results showed that AVG could provide a viable medical therapy for low back pain secondary to trauma-induced intervertebral disk degeneration. Orally administered rabbits groups halted and reversed disk degeneration in an annular puncture-induced disk degeneration rabbit model.

**Effects of aloe vera gel on aging-associated histological changes of the sciatic nerve**

Barmaki *et al*<sup>[37]</sup> investigated histological and histomorphometric changes of sciatic nerve in aged rats treated with aloe vera gel. The authors observed that some alterations in sciatic nerve caused by aging, such as accumulation of collagen in perineurium and endoneurium. And a significant decrease was seen in nerve fibers, nerve trunks diameter and myelin thickness, which were highly evident in rats of the 24 months age group. Treatment with aloe vera gel extract significantly improved histological changes and retarded neuropathy signs.

**MICRNAS AT THE INTERFACE BETWEEN OSTEOGENESIS AND ANGIOGENESIS AS TARGETS FOR BONE REGENERATION**

Bone formation and generation is a multistep complex process crucially determined by the formation of blood vessels in the growth plate region. This is preceded by the expression of growth factors, notably the vascular endothelial growth factor (VEGF), secreted by osteogenic cells. Thereby, coordinated coupling between osteogenesis and angiogenesis is initiated and sustained. Besides VEGF, micRNAs also support this key mechanism. Frolich L<sup>[38]</sup> elucidated that the molecular mechanisms governing bone angiogenesis are of great relevance for improving therapeutic options in bone regeneration, tissue-engineering, and the treatment of bone-related diseases.

**The histone deacetylase inhibitor butyrate improves metabolism and reduces muscle atrophy during aging**

Sarcopenia, the loss of skeletal muscle mass and function during aging, is a major contributor to disability and frailty in the elderly. A protective effect of reduced histone deacetylase activity in models of neurogenic muscle atrophy was found. Because loss of muscle mass during aging is associated with loss of motor neuron innervation, Walsh *et al*<sup>[39]</sup> investigated the potential for HDAC inhibitor butyrate to modulate age-related muscle loss. The authors found significant

loss of hind limb muscle mass in 26-month-old C57Bl/6 female mice fed a control diet. Butyrate treatment starting at 16 months of age wholly or partially protected against muscle atrophy in hind limb muscles. The authors showed a beneficial effect of butyrate on muscle mass during aging and suggested HDACs contribute to age-related muscle atrophy and may be effective targets for intervention in sarcopenia and age-related metabolic disease.

**THE PIVOTAL ROLE OF MICRNA-21 IN OSTEOCLASTOGENESIS INHIBITION BY ALOIN**

Madhyastha *et al*<sup>[40]</sup> investigated the role of miR-21 in aloin's inhibitory effect on osteoclast differentiation. Aloin effectively suppressed receptor activator of nuclear factor κ-B (NFκB) ligand-inducer miR-21 expression via repression of NFκB activation. Knockdown or gain-of-function studies revealed that miR-21 was pivotal to aloin's inhibitory effect on osteoclastogenesis.

**Aloin promotes osteogenesis of bone-marrow-derived mesenchymal stem cells**

Li *et al*<sup>[41]</sup> determined whether aloin promotes the proliferation and osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) and, if so, whether it acts via activation of ERK1/2-Runx2 signaling pathway. The authors demonstrated that aloin promotes osteogenic differentiation of BMSCs through activation of the ERK1/2-Runx2 signaling pathway.

**Aloin for ameliorating the progression of osteoarthritis**

Osteoarthritis (OA) is a progressive and degenerative joint disease. Zhang *et al*<sup>[42]</sup> investigated that aloin may inhibit the IL-1β-induced inflammatory response and promote extracellular matrix homeostasis in osteoarthritic chondrocytes. The effect of aloin on OA is through PI3K/Akt/NF-κB signaling pathway. In vivo study showed that aloin could ameliorate OA development in mice. Aloin might be a promising therapeutic strategy for the treatment of osteoarthritis.

**Case report 1: Useful aloe vera juice for the intestinal environment**

A 61-years-old frail woman who had hay fever ingested aloe vera juice during ten years. She is a sport instructor and was examined her intestinal microbiome by Microbiome Inc. on Sep. 2020. The comparative analysis of fecal *Clostridium*, *Faecalibacterium* and *Lactobacillus* showed 0.65%, 32.92%, and 0.83%, respectively, in which *Clostridium* is 2.4 fold higher, *Faecalibacterium* is 3.4 fold higher, and *Lactobacillus* is 2.0 fold higher, compared to the standard value of *Faecalibacterium*; 9.58%, *Clostridium*; 0.24%, and *Lactobacillus*; 0.40%, respectively. Both *Clostridium* and *Faecalibacterium spp.* is one of typical butyrogenic microbiome, exhibiting the potent immune regulative function. *F. prousnitzii* is one of the most abundant bacterial species in the colon of healthy human, and has been known as a major actor in human intestinal health and a biosensor.

Now she is no hay fever, well intestinal environment and QOL.

**Case report 2: Beneficial roles of aloe vera juice to migraine and movement**

Since 18-year-old she had migraine, nauseous, dizzy and ear noise. Doctor administered several medical treatments but she did not recover. She had two children after she become a nurse. When she was 40-year-old, she had a traffic accident on Oct. 2019. Then

her past medical history was clarified to be Chiari malformation syringomyelia. The doctor administered anti-inflammatory analgesic and muscle-relaxant, and recommended a large exhalent decompression, but she denied take drugs and surgery. She started to ingestion of AVJ 1500ml/day since Dec. 2019. Now she is no migraine and nauseous, and has a well movement with QOL.

## CASE REPORT DISCUSSION

In preliminary case report<sup>[43]</sup> we reported that the subjects having pain troubles more than 32 points in locomotive syndrome risk test decreased after ingestion of the supplement (curcumin, enzyme hydrolyzed eggshell membrane, and L-arginine) with aloe vera juice (AVJ) in a ratio of 13.9%, and the subject having in daily pain troubles less than 14 points decreased to 70.2%. No side effect from consuming the supplement was confirmed. Furthermore we presented that treatment of Parkinson's disease (PD) drug with  $\omega$ -3PUFA, L-arginine, and AVJ improves cognition and muscle stretching. For instance the PD patients with diabetes at stage 3 were in remission PD-stage 2 by treatment of PD-drug and  $\omega$ -3PUFA/L-arginine with AVJ after the treatment of several months and the patient at PD-stage 3 were in remission PD-stage 0 by the treatment of PD-drug with  $\omega$ -3PUFA, L-arginine with AVJ after two months. Efficacy of nutraceutical AVJ as an adjuvant with the supplement was fully expected for mitigation of locomotive syndrome risk and risk factors in PD patients with/without diabetes. PD may begin with the intestinal accumulation of  $\alpha$ -synuclein fibrils, which can be causally associated with gutbionosis.

Nishiwaki *et al*<sup>[44]</sup> reported that intestinal mucin layer-degrading *Akkermansia* spp. is increased and that SCFA-producing *Roseburia* spp. and *Faecalibacterium* spp. are decreased in Parkinson's disease across counties. The butyrogenic gut commensal bacteria (*Faecalibacterium*, *Clostridia*, *Butyrivibrio* etc.) ferment pyruvate for butyrate production. *F. prausnitzii* (an anti-inflammatory bacterium) is one of most abundant bacterial species in the colon of healthy human. In a case report 1 the ingestion of AVJ for seven-years in 61-years old frail female increased 3.4 fold higher in the comparative fecal content of butyrogenic prebiotic *Faecalibacterium* spp. She is no hay fever and well QOL.

Kong *et al*<sup>[45]</sup> reported that cohort study of long-living people possesses a more diverse gut microbiota than younger adults, and found a group of bacteria, members of which are known SCFA producers; *Clostridium* cluster XIVa, are enriched in long-living Chinese and Japanese. Zuo *et al*<sup>[46]</sup> reported that fecal microbiomes from patients with COVID-19 had depletion of commensal symbionts (*Eubacterium*, *Faecalibacterium*, *Roseburia*, *Lachnospiraceae*) and enrichment of opportunistic pathogens (*Bacteroides*), which persisted after clearance of SARS-CoV-2. Baseline microbiome composition associated with COVID-19 severity. Multiple species from the *Bacteroidetes* phylum correlated inversely with fecal shedding of SARS-CoV-2. Strategies to alter the gut microbiome might be developed to manage gastrointestinal effects of the virus in these patients.

In a case report 2 the long-term ingestion of AVJ for 41-years old female having Chiari malformation syringomyelia, provided a well QOL. The results showed that AVJ could play a role as a beneficial herbal medicine for a promising tool to tissue repair and bone regeneration.

## SUMMARY

Present review is focused on aloe components, short chain fatty acids

butyrate, and miRNAs to prevent Alzheimer's disease (AD) and Parkinson's disease (PD). It was suggested that aloe components, butyrate fermented, and miRNAs modulate senescence-related pathological conditions.

Modulation of the gut microbiota through a personalized diet or beneficial microflora intervention like pro/prebiotics, changing microbiological partners and their products, including amyloid protein, can become a new treatment for AD. Nearly 50% of patients with PD exhibit symptoms of constipation, which often precedes the diagnosis of PD and onset of motor deficits, and constipation may be a risk factor for later development of the disease. It is suggested that the PD-associated microbiota may harbor microbes and functions that drive this neurodegenerative disease.

Present manufacturing process of hyaluronic acid (HA) requires extraction of animal cells or through other methods utilizing bacteria. As an alternative source of HA extraction using plant based, aloe vera endophytic bacteria was investigated<sup>[31]</sup>. In the earlier report fermentation by endophytic bacteria in aloe vera gel provided short chain fatty acid, butyric acid<sup>[47]</sup>. Daily intake of the fermentation extract from Aloe vera with endophytic bacteria may provide the possible potential preventive roles in human health.

Furthermore two case reports suggested that aloe vera juice successive ingestion keeps healthy life and well QOL through the intestinal production of prebiotic butyrogenic gut microbiome, *Faecalibacterium* spp., and could play a beneficial role for tissue repair and bone regeneration.

The present review elucidates big evidence of aloe vera as a prophylactic medicinal herb on gut-brain-osteogenesis.

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