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Review Article

Prophylactic Role of Fermented Butyrate to Alzheimer's and Parkinson's Disease-Like Neuro-Disorders and Plant-Derived Extracellular (Plant Exosome)-Like Vesicles in *Aloe vera* as an Useful Carrier in Drug Delivery Systems

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Abstract

Humans' diseases such as Alzheimer's disease and Parkinson's-like neuro-disorders may retain an epigenetic etiology, and new therapeutic option termed as "epigenetic therapy" can offer a potential way to treat these diseases. Among epigenetic agents the inhibitor of histone deacetylase butyrate fermented in *Aloe vera* gel and expression of plant-derived extracellular (plant exosome)-like vesicles in *Aloe vera* as a carrier of micRNA in drug delivery systems are discussed in the present review.

Keywords: *Aloe vera; Alzheimer's Disease (AD); Parkinson's Disease (PD)*

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders and are characterized by deposition of specific proteins in the brain. If similar abnormal protein deposits are present in the eye, it would facilitate noninvasive diagnosis and monitoring of disease progression. Ho., *et al*. [1] evaluated expression of proteins associated with AD and PD pathology in postmortem eyes and brains in a case-control study. No amyloid deposits or abnormal tau accumulations were detected in the lens, retina or other structures in the eyes of AD patients. The results suggested that β-amyloid, phosphor-tau and α-synuclein either do not deposit in the eye in a manner analogous to brain or are present at lower levels or in different forms. To clarify any association of short- and medium-chain fatty acid intake with cognitive decline, Otsuka., *et al*. [2] studied 298 men and 272 women aged 60 years and older at the baseline who participated at least once in the follow-up study of National Institute for Longevity Sciences-Longitudinal Study of Aging. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). Nutritional intake was assessed using a 3-day dietary record. The multivariate-adjusted odds ratios (MAOR) for a decline in MMSE score (≤ 27) was 0.86 (95%confidence intervals (CI) for an MMSE score of 27 (cognitive score decline) in each study wave according to a 1 standard deviation (SD) increase of short, medium and long-chain fatty acid (SCFA; MCFA and LCFA) intake at the baseline were estimated after adjusting for sex, age, follow-up time and other covariates. The MAOR for a decline in MMSE score (≤ 27) was 0.86 (95%CI: 0.75 - 0.98) with a 1 standard deviation increase intake of SCFAs (181 mg/day), 0.84 (0.74 - 0.95) for MCFAs (232 mg/day), and 0.89 (0.76 - 1.04) for LCFAs (181 mg/day). SCFAs (butyrate) and MCFAs intake may prevent cognitive score decline in community dwelling elderly.

MicroRNAs (miRNAs) are an abundant class of newly identified endogenous non-protein-coding small RNAs. They exist in animals, plants and viruses and play an important role in gene silencing [3]. Extracellular vesicles (exosome) derived from plants could be useful for drug delivery systems. The administration of miRNA and exosome-like nanoparticles mixture in cells achieved downregulation of the miRNA's target gene, and this mixture showed cytoplasmic localization indicating potential use as a drug delivery system for nucleic acid medicine. Acerola (popular health food) exosome-like nanovesicles to systemically deliver nucleic acid medicine via oral administration was investigated by Umezu., *et al* [4].

Present review is focused on prophylactic role of fermented butyrate in *Aloe vera* to AD and PD-like neuro-disorders and extracellular/plant exosome-like vesicles in *Aloe vera* as a useful carrier of micRNA in drug delivery systems.

A histone deacetylase inhibitor butyrate rescued wild type α-synuclein-induced DNA damage

α-Synuclein (α-Syn) is considered a major culprit in Parkinson's disease (PD) pathophysiology. Paiva., *et al*. [5] evaluated the impact of wild type (WT) and mutant A30P α-Syn on gene expression, in a dopaminergic neuronal cell model, and decipher potential mechanisms underlying α-Syn-mediated transcriptional deregulation. The author performed gene expression analysis using RNA-sequencing in Lund Human Mesencephalic cells expressing endogenous (control) or increased levels of WT or A30P α-Syn. A histone deacetylase inhibitor butyrate rescued WT α-Syn induced DNA damage, possibly via upregulation of genes involved in DNA repair.

Butyrate can attenuate pro-inflammatory cytokine expression in microglia in aged mice

Aging results in chronic systemic inflammation that can alter neuro-inflammation of the brain. Specially, microglia shift to pro-inflammatory phenotype predisposing them to hyper-activation upon stimulation by peripheral immune signals. Matt., *et al*. [6] demonstrated that butyrate can attenuate pro-inflammatory cytokine expression in microglia in aged mice. And histological scoring of the distal colon demonstrated that aged animal on the low fiber diet had increased inflammatory infiltrate that was significantly reduced in animals consuming the high fiber diet. Furthermore, gene expression of inflammatory markers, epigenetic regulators, and the microglia sensory apparatus were altered by both diet and age, with aged animal exhibiting a more anti-inflammatory microglial profile on the high fiber diet. High fiber supplementation in aging is a non-invasive strategy to increase butyrate levels, and these data suggested that an increase in butyrate through added soluble fiber could counterbalance the age-related microbiota dysbiosis, potentially leading to neurological benefits.

An association between certain bacterial strains and Alzheimer's disease

Marizzoni., *et al*. [7] investigated the association between amyloid pathology, bacterial products such as lipopolysaccharides (LPS) and short chain fatty acids (SCFAs), inflammatory mediators and markers of endothelial dysfunction in AD. The results showed that amyloid standard uptake value ratio uptake was positively associated with blood LPS, acetate and valerate, pro-inflammatory cytokine and biomarkers of endothelial dysfunction. In contrast, it was negatively correlated with butyrate and the anti-inflammatory cytokine IL-10 levels. In conclusion, the author 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 link between the gut microbiota and AD pathology.

Significant overlap of α-synuclein, amyloid-β, and phosphor-tau pathologies in neuropathological diagnosis of Lewy-related pathology

Lewy-related pathology (LRP), primarily composed of α-synuclein, is a typical neuropathological change that has been identified in many neurodegenerative disorders such as Parkinson's disease (PD), PD with dementia, and dementia with Lewy bodies. Cong., *et al*.

[8] investigated the distribution of LRP in the China Human Brain Bank, the co-occurrence of neuro-pathologic features of Alzheimer's disease (AD) in LRP cases, and LRP-related cognitive dysfunction. In conclusion, the author showed that the overlap of neocortical α-synuclein, amyloid-β, phosphor-tau, and neuritic plaques in LRP suggested the potential interplay among the common characteristics of proteinopathies in the late stage of neuropathological development of LRP in human brains. The anatomic progression of LRP, the process of α-synuclein spreading from the brainstem to limbic and neocortical regions, might aggravate the deterioration of cognitive function in addition to that effect of AD.

The role of the gut microbiota in modifying Alzheimer's disease (AD) progression

The mechanisms of microbiome-brain interaction in AD were identified by Colombo., *et al* [9]. Germ-free (GF) AD mice exhibited a substantially reduced amyloid β (Aβ) plaque load and markedly reduced short chain fatty acid (SCFA) plasma concentration; conversely, SCFA supplementation to GF mice increased the Aβ plaque load to levels of conventionally colonized specific pathogen-free (SPF) animals and SCFA supplementation to SPF mice even further exacerbated plaque load. This was accompanied by the pronounced alteration in microglial transcriptomic profile, including upregulation, microglia contained less intracellular Aβ. The results demonstrated that microbiota-derived SCFA are critical mediators along the gut-brain axis which promote Aβ deposition likely via modulation of the microglial phenotype.

The changes in the gut microbiome and associated metabolites are related to PD symptoms

Stool, whole blood samples, and clinical data were collected from 55 PD patients and 55 controls and analyzed DNA methylation on whole blood samples and microbiome composition by Xie., *et al* [10]. The author found that lower level butyrate and reduced counts of genera *Roseburia, Romboutsia* and *Prevotella* are related to depressive symptoms in PD patients. Gene containing butyrate- associated methylation sites included PD risk genes and significantly overlap with sites epigenetically altered in PD blood leucocytes, predominantly neutrophils, and in brain neurons, relative to controls. And butyrate-associated methylation-DNA regions in PD overlap with those altered in gastrointestinal (GI), autoimmune, and psychiatric diseases. Decreased levels of bacterially produced butyrate are related to epigenetic changes in leucocytes and neurons from PD patients and to the severity of their depressive syndromes. PD shares common butyrate–dependent epigenetic changes with certain GI and psychiatric disorders, which could be relevant for their epidemiological relation.

Comparison of fecal and plasma levels of different short chain fatty acid (SCFA) subtypes in patients with parkinson's disease (PD) and healthy controls to delineate their interrelations and link to gut microbiota changes and clinical severity of PD

A cohort of 96 patients with PD and 85 controls were recruited from National University Hospital. Fecal and plasma concentrations of SCFAs were measured by Chen., *et al*. [11] using chromatography and mass spectrometry. SCFAs producing gut bacteria correlated positively with fecal levels of SCFAs in healthy controls but revealed no association in patients with PD. In the PD patients the abundance of pro-inflammatory microbes, such as *Clostridiales bacterium* NK3B98 and *Ruminococcus* sp. AM07-1S, significantly correlated with decreased fecal levels and increased plasma levels of SCFAs, especially propionic acid. Reductions in fecal SCFAs but increased plasma SCFAs were observed in patients with PD and correlated to specific gut microbiota changes and the clinical severity of PD.

Identification of *Faecalibacterium prausnitzii* strains for gut microbiome-based intervention in Alzheimer's type dementia

Relationship between specific microbes and cognitive function in mild cognitive impairment (MCI) was analyzed by Ueda., *et al* [12]. The author found that *Faecalibacterium prausnitzii* (*F. prausnitzii*) correlated with cognitive scores and decreased in the MCI group compared with the heathy group. Two isolated strains from the healthy group, live Fp360 and pasteurized Fp14, improve cognitive impairment in an AD mouse model. Whole-genome comparison of isolated strains revealed specific orthologs that are found only in the effective

strains and are more abundant in the healthy group compared with the MCI group. The author concluded that *F. prausnitzii* strains with these specific orthologs are candidates for gut microbiome-based intervention in Alzheimer's-type dementia.

Aloe-derived exosome-like nanovesicle as a functional carrier in drug delivery system

Plant exosome-like nanovesicles, being innately replete with bioactive lipids, proteins, RNA, microRNA and other pharmacologically active molecules, offer unique morphological and compositional characteristics as natural nanocarriers. Extracellular vesicles (EVs) derived from plants have emerged as potential candidates for therapeutic applications. Kim., *et al*. [13] isolated EVs from *Aloe vera* peels (A-EVs) and investigated the antioxidant and wound healing potential of A-EVs. A-EVs were isolated by ultracentrifugation and tangential flow filtration and were characterized using transmission electron microscopy, nanoparticle tracking analysis. The cytotoxicity and cellular uptake of A-EVs were investigated by WST-1 assay and flow cytometry. A-EVs displayed a round shape and had diameters from 50 to 200 nm. A-EVs showed good cytocompatibility on human skin cells and were internalized into human keratinocytes cells via clathrin, caveolae-mediated endocytosis, and membrane fusion. The author revealed that A-EVs could activate the antioxidant defense mechanisms and wound healing process via the nuclear factor erythroid 2–related factor 2, Nrf2, activation. The author demonstrated that A-EVs are promising as a potential agent for skin regeneration.

Aloe-derived nanovesicle as a functional carrier for indocyanine green encapsulation and phototherapy

Zeng., *et al*. [14] isolated nanovesicles from the gel and rind of *Aloe vera* (gADNVs and rADNVs) with higher quality and good yield by controlling the final centrifugation time within 20 minutes and modulating the viscosity at 2.98 mPaS and 1.57 mPa S, respectively. They could be efficiently taken up by melanoma cells and with no toxicity *in vitro* or *in vivo*. Indocyanine green (molecular weight; 775, cancer therapy drug, ICG) loaded in gADNVs (ICG/ADNVs) showed great stability in both heating system and in serum, and its retention rate exceeded 90% after 30 days stored in gADNVs. ICG/gADNVs stored 30 days could still effectively damage melanoma cells and inhibit melanoma growth, outperforming free ICG liposome. gADNVs showed prominent penetrability to mice skin which might be beneficial to noninvasive transdermal administration.

Aloe saponaria-derived extracellular vesicles and their potential for chronic wound healing

Neutral polysaccharides that inhibit carrageenan induced edema in rats were isolated from the non-dialysate of the pulp of *Aloe saponaria* by gel filtration [15]. Kim., *et al*. [16] isolated extracellular vesicles (EVs) from *A. saponaria* by polyethylene glycol-based precipitation and investigated their potential as a therapeutic for chronic wound healing. The *A. saponaria* derived EVs (AS-EVs) showed no significant cytotoxicity on several cell types. AS-EVs enhanced tube formation in human umbilical vein endothelial cells, indicating a stimulatory activity on angiogenesis; one of the crucial steps for effective wound healing. The results suggested that the potential of AS-EVs as a natural therapeutic for chronic wound healing.

The development of plant exosome-like nanovesicles to clinical application: the feasibility of orally administrated nucleic acid drug delivery by acerola exosome-like nanoparticles

Acerola (*Malpighia emarginata* DC.) is a popular health food. Umezu., *et al*. [4] examined the feasibility of orally administered nucleic acid drug delivery by use of acerola exosome-like nanoparticles (AELNs). AELNs were recovered from acerola juice using an affinity column instead of ultracentrifugation. MicroRNA (MiRNA) was sufficiently encapsulated in AELNs by 30-minutes incubation on ice and was protected against RNase, strong acid and base treatments. The administration of AELNs/miRNA mixture in cells achieved downregulation of the miRNA's target gene; and this mixture showed cytoplasmic localization. AELNs orally delivered small RNA to the digestive system *in vivo*. The target gene-suppressing effect in the small intestine and liver peaked 1 day after administration, indicating potential for use

as an oral drug delivery system for nucleic acid medicine in the digestive system. These is an increased trend in the number of approved nucleic acid therapeutics in drug delivery systems, with regards to clinical application.

The pivotal role of micRNA-21 in osteoclastogenesis inhibition by aloin in *Aloe vera*

MicRNAs are emerging as key plyers in bone remodeling, modulating the functions and both osteoblasts and osteoclasts. Among them, miRNA-21 is highly expressed in osteoclast precursors and is known to regulate genesis, differentiation, and apoptosis of osteoclasis. Aloin, the active ingredient derived from *Aloe* spp. is of great medical value and a quality standard compound based on Japanese Pharmacopoeia. In the previous paper [17] prophylactic role of histone deacetylase inhibitor butyrate and micR-21 in *Aloe vera* to cancer prevention was described. Several studies established the crucial role of micRNA-21 (miR-21) within aloin-mediated inhibition of osteoclast formation. Aloin effectively suppressed receptor activator of nuclear factor kappa-B (NFκB) ligand (RANKL)-induced miR-21 expression via repression of NFκB activation. MiR-21 suppression resulted in up-regulation of osteoclast suppressor for programmed cell death protein 4 and down regulation of osteoclast marker cathepsin K. Knockdown or gain-of-function studies revealed that miR-21 was pivotal to aloin's inhibitory effect on osteoclastogenesis. The dynamic potential of aloin as a therapeutic agent to treat osteopenia via miRNA-21 expression was highlighted by Madhyastha., *et al* [18].

Summary

We discussed the current knowledge focusing on the influence of histone deacetylase inhibitor (HDAC) butyrate in *Aloe vera* gel and plant extracellular (plant exosome)-like vesicles in *Aloe vera* by which the gut-microbiota is beneficial for behavior to gut-brain homeostasis. Specially, the isolation of Aloe saponaria-derived extracellular vesicles having chronic wound healing [16] and the pivotal role of miRNA-21 in osteoclastogenesis inhibition by aloin in *Aloe vera* [18] may provide a competent influence to osteoarthritis and wound healing. Butyrate fermented in *Aloe vera* as a HDAC inhibitor could impact brain health and plant derived exosome in *Aloe vera* are emerging key players in wound healing.

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