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REVIEW

Putative Roles of Aloe Ingredients in Aging and Age-Related Diseases: Management of Microbiota Senoinflammatory Process

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ABSTRACT

Aging and age-related diseases of increasing elderly population are the most challenging biomedical problem at present. Age-related chronic inflammatory diseases, metabolic syndrome, diabetes, kidney disease, osteoporosis, and dementia are common occurrences among the elderly. In this review, we described putative roles in intestinal homeostasis by butyrate, evaluation of aloe constituents, on prevention of leaky gut syndrome due to age-related increased intestinal permeability which can lead to many systemic inflammatory

and immune-related dysfunctions. Our presentation on the beneficial efficacy of aloe ingredients were discussed based on management of gut microbiota and age-related senescent inflammation, known as senoinflammation.

Key words: Putative roles; Aloe ingredients; Butyrate fermented; Senoinflammatory process

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INTRODUCTION

Phytochemicals from plants played important roles in maintenance of health and attenuation of various diseases through our human history. One of such well known phytochemicals is aloe. It has been demonstrated that life-long ingestion of aloe vera by laboratory rats exhibited a wide-range of modulation of various age-related hormonal, metabolic changes and beneficial against the age-related pathology^[1]. The remedial use of aloe plants for chronic in the remedy of chronic inflammation has been publicized in the past, and the major aloe ingredients on their efficiency related to the immune modulating activities was reviewed recently by us^[2]. Chronic low-grade systemic inflammation during normal physiological aging and immuno-senescence are causally related with the pathogenesis of premature aging. The immune-senescence is a well-recognized factor associated with frailty, morbidity, and mortality in elderly subjects. Human aging is characterized by a chronic, low-grade inflammation, and this age-related senescent inflammation has recently been termed as “senoinflammation” by Chung et al^[3]. Human diet is believed to have a major influence on both the development and prevention of age-related diseases. Therefore assessment and proper support of gastrointestinal function may provide benefit for elderly people with a variety of

chronic complaints. Microbiota and products thereof: short-chain fatty acids and quorum sensing signal molecule, are indispensable for shaping the development and function of host innate immune system, thereby exerting the multifaceted impacts on gut health. Although immunity influenced by heritability and the environment is well-known, but how these factors synergize to influence immune function is not well characterized at present.

Most plant-derived dietary phytochemicals and macro- and micro-nutrients modulate oxidative stress and inflammatory signaling and regulate metabolic pathways and bioenergetics that can be translated into stable epigenetic patterns of gene expression. Senoinflammatory process during physiological aging and influenced by dietary patterns reveal the complexity of epigenetic changes through lifetime^[4]. Sintouo *et al*^[5], based on evidence reported in the literature on the association between chronic inflammation and gut microbiota during aging. PubMed, Web of Science and Scopus were systematically screened, concluded that the chronic gut inflammation is causally associated with changes in gut microbiota. The fecal microbiota plays an important role in human health, and alterations in the microbiota-host interaction seem to be involved in the ageing process. It is important to develop strategies for promoting a balanced microbiota in old age in order to prevent the physiological and immune decline associated with aging. Salazar *et al*^[6] assessed the level of some intestinal microbes and short chain fatty acids across different age-groups. Aging was associated with a progressively and statistically significant reduction in the fecal concentrations of short chain fatty acids. The results underline the better understanding the aging and immunosenescence processes by a close monitoring of the profound impact of the microbiota.

Epigenetic factors, such as lifestyle and diet, are shown to be essential in the control of human healthy aging, and thus, longevity. Ragonnaud and Briagyn^[7] provide evidence that gut dysbiosis triggers a chain of pathological and inflammatory events. Examples include alteration of levels of microbiota-affected metabolites, impaired function and integrity of the gastrointestinal tract, and increased gut leakiness. All of these enhance systemic inflammation, which when associated with aging is known as senoinflammation, and result in consequent aging-associated pathologies.

Diet is a natural source of butyrate through the fermentation of non-digestive fiber, such as acemannan in aloe vera gel, is an important ingredient for health and quality of life as an immune modulation in aged people. Long-term dietary intake of non-calorie fiber, such as aloe vera gel influences the structural and activity of microorganisms in the human gut. Fermentation by endophytic bacteria, such as *Lactobacillus fermentum*, in aloe vera gel provided butyric acid, suggesting that the daily application of fermented aloe vera gel extract may be benefit for health and as an immune modulator^[8,9]. In HPLC analysis of Aloe species^[10], the phenolic compounds increased clearly in the order: base, center and point, suggesting the relation to the part of the leaf decreases with age in aloe. Furthermore, previous review^[11,12] described health benefit of long-term ingestion of aloe vera gel through the modification of the intestinal microbiota, and aloe vera gel ingestion related to attenuation of reactive oxygen species, prevention of cardiovascular disorders, and effects of life-prolonging calorie restriction^[13]. Alterations of gut microbiota may be accompanied by altered concentrations of short chain fatty acids, such as butyric acid. Thus, interventions that alter the composition of the gut microbiota may well reduce pro-inflammatory state and rejuvenate immune functions to provide anticancer and insulin secretion benefits in frail elderly people. Intestinal microbiota producing butyrate might be developed for the therapeutic purpose to increase

insulin sensitivity in humans with calorie restriction. The digestion of fermented extract of aloe vera gel may be beneficial for health and quality of life as an immune modulator in frail elderly people.

Based on what is known about the unique function of gut microbiota, it should be considered a potent hidden metabolic organ of the human body to provide metabolically essential biochemical functions that needed for the maintenance of healthy aging of elderly people. Senoinflammatory process, microbiota, gut integrity are all inter-dependently related by sharing common/or similar mechanistic processes.

In the present review, we elaborate on prophylactic effect of aloe constituents, high molecular materials, and butyrate fermented, on senoinflammatory process in healthy aging of elderly people and leaky gut prevention by aloe and butyrate. Nutritional and prophylactic aloe ingredients for restoring the gut integrity by reducing changes in inflammation, gut microbiota to blood-brain barrier permeability, and leaky gut prevention by aloe and butyrate were extensively discussed. Furthermore micRNA-146a and -21 were noted as the new disease-biomarkers of senoinflammatory process (Figure 1).

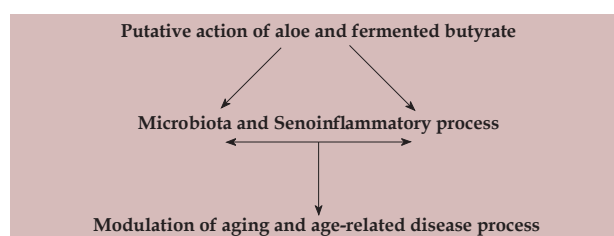


Figure 1 Putative roles of Aloe and fermented butyrate for modulation of aging and age-related disease process.

ANTI-INFLAMMATORY PROPERTY OF ALOE, ALOESIN, ALOIN, AND ALOE-EMODIN

Inhibition by Aloe leaves extracts of L-dopa oxidation by mushroom-tyrosinase was examined. 2'-O-Feruloylaloenin and aloesin at concentrations of 0.4 μ M showed inhibition of 27 and 30%, respectively^[14]. Modulation of melanogenesis via competitive inhibition of tyrosinase by aloesin was demonstrated^[15]. These data suggest the possible efficacy against photo-aging by aloesin and its derivative in Aloe leave extract.

Aloesin treatment accelerated wound closure rates in hairless mice by inducing angiogenesis, collagen deposition and granulation tissue formation. And aloesin treatment resulted in the activation of Smad and MAPK signaling proteins that are key players in cell migration, angiogenesis and tissue development. These findings indicate that aloesin has the therapeutic potential for treating cutaneous wounds^[16].

Park *et al*^[17] compared the anti-inflammatory effects; the levels of iNOS mRNA expression and NO production of aloe and aloemodin at 5-40 μ M, with other polyphenols. Furthermore the levels of COX-2 mRNA and PGE2 production were suppressed by 40 μ M aloe-emodin. The results indicated that aloe and aloemodin possibly suppress the inflammatory responses by blocking iNOS and COX-2 mRNA expression. The anti-inflammatory property of aloe-emodin may be a major key constituent responsible for the anti-inflammatory activity of aloe plant extract.

Cho *et al*^[18] investigated whether dietary aloe vera gel has anti-aging properties on the skin. Aloe vera gel significantly improves wrinkles and elasticity in photo-aged human skin with an increase in collagen production in photo-protected skin and a decrease in the collagen-degrading matrix metalloproteinase-1 gene expression.

Zhong *et al*^[19] investigated the protective effects and underlining

mechanisms of aloin on D-galactose induced aging mice. Aloin treatment significantly ameliorated histopathological damage, attenuated the microglia activation and reduced levels of inflammatory mediators, such as TNF- α , IL-1 β and IL-6 in the hippocampus. The protective effects were achieved by inhibition of the activation of proinflammatory NF- κ B and the phosphorylation of p38 and ERK.

Gokulan *et al.*^[20] investigated the antibacterial effects, butyrate-production in fecal microbacteria, and trans-epithelial resistance results. The authors concluded that (1) Aloin exhibits antibacterial properties for certain intestinal commensal bacteria; (2) Aloin decreases the butyrate production in dose dependent manner; (3) Aloin alters the intestinal epithelial cells barrier integrity at 500 μ M concentration in pH 4.9. Trans-epithelial resistant result revealed that aloin alters the intestinal barrier-function at higher concentration.

ALOE VERA HYALURONAN AS A KEY PLAYER IN REGULATING INFLAMMATION

Skin aging is correlated with loss of skin moisture that is maintained by hyaluronan (HA, hyaluronic acid), a glycosaminoglycan, having the properties of binding and retaining water molecules. During aging, HA present in the skin diminishes leading to the dry and wrinkled skin. HA is an important component of active pharmaceutical ingredient for treatment of arthritis and osteoarthritis declining with aging. HA has been produced via microbial (*Streptococcus zooepidermicus*, *Bacillus subtilis* and others). Putri *et al.*^[21] found HA on Aloe vera just below the waxy cuticle of rind and there is an area where aloe correlated bacteria lives. Gram-positive microbe *Streptococci* which are able to produce HA through bacterial pathway were only found on the surface of aloe vera, while *Cocobacilli* (*Staphylococcus morbilloium*, *Enterococcus faecium*, and other Gram-negative rods) are observed only in the gel part.

HA, a major component of the extracellular matrix plays a key role in regulating inflammation. Inflammation is associated with accumulation and turnover of HA polymers by multiple cell types. HA and its binding proteins regulate the expression of inflammatory genes, the recruitment of inflammatory cells, the release of inflammatory cytokines, and can attenuate the course of inflammation, providing protection against tissue damage. Petrey and de la Motte^[22] focused on the role of HA in the promotion and resolution of inflammation.

ALOE ACEMANNAN FOR IMMUNE AND GUT MICROBIAL MODULATION

Aloe polysaccharide, acemannan, for age-related diseases and its check items are generally known traditional and specific diseases followed by *in vitro*, animal and preclinical studies: (1) Prevention of cancer and alleviation of progeria; (2) Prevention of cardiovascular and cerebrovascular disorders, and inhibition of acetylcholine esterase; (3) Preliminary clinical study of an aloemnanose multi-nutrient complex on cognitive and immune function in Alzheimer's disease, (4) Prevention of photo-aging and polycystic ovarian syndrome, (5) Stimulation of periodontal fibroblasts, (6) Anti-inflammation and immune-response enhancing diabetic and hepatic disorders^[23]. Acemannan as an adjuvant may interact and activate various toll-like receptors and inflammasomes, involving several innate immune system players in the ensuring immune response. The gut microbiota had defined new milestones for understanding the microbial ecology of the gastrointestinal ecosystem and accessing

how the microbial world within us impacts our everyday life. In previous paper, we documented the immune modulation and gut microbiota influence by aloe vera, acemannan^[24]. The beneficial effects of endophytic butyrate productions, delivery, and absorption by colonocytes have been demonstrated in previous paper^[25]. Acemannan has been shown to activate macrophages and stimulate T cells that are involved in the defense against harmful micro-organisms by likely acting as an adjuvant for health and disease. Commercially available acemannan preparation used for these studies often contains a complex mixture of about 60% acetylated mannan together with other carbohydrates, pectin, hemicellulose, lectins, and protein.

THE INFLUENCES OF GUT MICROBIOTA TO BLOOD-BRAIN BARRIER PERMEABILITY

Pivotal to brain development and function is an intact blood-brain barrier (BBB), which acts as gatekeeper to control the passage and exchanges and nutrients between the circulatory system and the brain parenchyma. Braniste *et al.*^[26] reported that germ-free mice, beginning with intrauterine life, displayed increased BBB permeability compared to pathogen-free mice with a normal gut flora.

The results strongly suggested that gut-microbiota-BBB interaction is initiated during gestation and propagated throughout life. The authors evaluated BBB permeability in germ-free adult mice mono-colonized with a single bacterial strain, *Clostridium tyrobutyricum* that produces mainly butyrate, and more interestingly, reported that administration of sodium butyrate was associated with an increase in histone acetylation in brain lysates and prevented BBB breakdown and promoted angiogenesis and neurogenesis.

BENEFICIAL EFFECTS OF ALOIN AND BUTYRATE FOR LEAKY GUT SYNDROME

The role of the gut mucosa as the preventive cell layer and the gastrointestinal promoting permeability

The cells in the intestinal epithelium form tight junctions or connections between each other. These tight junctions constitute a barrier between the molecules within the lumen of the intestinal tract and the inside of the body. Host intestinal barriers include physical barrier, biomedical barrier, and immunological barrier. Under normal healthy conditions, these barriers do not allow flow of matter from the outside lumen to the inside of the body, unless the matter goes through a cell. Without the barrier molecules of all types are able to go around the cells and get into circulation. The condition is known as intestinal permeability or "leaky gut"^[27]. Intestinal permeability is commonly seen in patients with intestinal inflammation and food allergies. Endogenous toxins such as bacterial and fungal by-products produced by resident flora and exogenous toxins such as food additives and alcohol can negatively influence intestinal integrity to increase intestinal permeability^[28].

Small intestinal and gastrointestinal permeation-enhancing aloe vera gel

Kim *et al.*^[29] investigated the anti-ulcer effects of aloe vera on the small intestine, especially focusing on mucin expression. The results indicated that processed aloe vera gel (PAG) treatment attenuates not only the severity of intestinal ulcers but also bacterial translocation, by enhancing the mucin layer in the indomethacin-induced small intestinal damage mouse model. The authors proposed that PAG application is a potential strategy for the alleviation of nonsteroidal anti-inflammatory drugs-induced small intestinal ulcers. Pretorius *et*

al^[30] aimed to investigate the insulin permeation enhancing effects of aloe vera gel across excised pig intestinal tissues from different regions of the gastrointestinal tract and to identify the gastrointestinal region where the highest insulin permeation enhancement. The gastrointestinal permeation enhancing effects of aloe vera gel on insulin is region specific with the highest effect observed in the ileum and colon.

The role of aloin in the protection against intestinal permeability

Gokulan *et al*^[20] reported the antibacterial effects, butyrate-production in fecal micro-bacteria and trans-epithelial resistance results. The authors furthermore demonstrated that aloin induced cytotoxicity in intestinal epithelial cells required at least two times higher concentration than the effect observed in Jarkat T-lymphocytes. The possible mechanism may involve intestinal epithelial cells secreting mucin, which could serve as a protective layer and prevent immediate interaction with epithelial cells. In contrast, T-lymphocytes lack a mucus layer, and aloin may interact with T-cells more quickly and require a smaller aloin concentration to induce cytotoxicity. Trans-epithelial resistance results positive evidence that aloin dissolved at concentration of 500µM in pH 4.9 compromised the intestinal barrier function (trans-epithelial resistance) in a dose-dependent manner. Aloin altered the intestinal epithelial cells barrier integrity.

The role of short chain fatty acid, butyrate, enhancing the intestinal barrier by facilitating tight junction integrity

Peng *et al*^[31] determined the effect of butyrate on the intestinal barrier by measuring the trans-epithelial electrical resistance (TER) and inulin permeability in a Caco-2 cell monolayer model. The authors used a calcium switch assay (assessed by the junctional resealing, i.e., increased TER on Ca²⁺ replacement) to study the assembly of epithelial tight junctions and determined the effect of butyrate on the assembly of epithelial tight junctions and AMP-activated protein kinase (AMPK) activity and accelerated the assembly of tight junctions, as well as the development of TER. AMPK activity was also upregulated by butyrate during calcium switch-induced tight junction assembly.

THE REGULATION OF INTESTINAL HOMEOSTASIS BY MICROBIOTA-DERIVED BUTYRATE

Inflammatory insult damages the intestinal epithelium in which necessitate mucosal wound healing for successful resolution. Disruption of the intestinal epithelial barrier, commonly observed in mucosal inflammation is a critical issue in inflammatory bowel disease (IBD). Restoration of epithelial barrier cellular is decisive for inflammatory resolution. Wang *et al*^[32] showed that short chain fatty acids levels were reduced in chronic kidney disease (CKD) patients and that butyrate supplementation might delay CKD progression. Wang *et al*^[33] identified a cluster of actin-associated genes regulated by butyrate, and showed the selective induction of the actin-binding protein synaptopodin as an intestinal tight junction protein with a central role in epithelial barrier regulation. These findings established that a fundamental role for the microbiota and the metabolite butyrate regulates intestinal homeostatic intestinal mucosal function through regulation of actin-associated protein synaptopodin. As butyrate regulation of the intestinal mucosa is multifaceted and can influence not only the epithelial cells but also immune cells, the results contribute to an evolving role for short chain fatty acids in mucosal homeostasis. Butyric acid promoted epithelial wound-healing responses.

MICRNA AS A NEW BIOMARKER OF SENOINFLAMMATION PROCESS

A major issue in aging research is how cellular phenomenon affects aging at the systemic level. Emerging evidence suggests that DNA damage response (DDR) signaling is a key mechanism linking DNA damage accumulation, cell senescence, and organism aging. The buildup of cells with an activated DDR probably fuels chronic inflammation and predisposes to the development of the major age-related diseases (ARDs). MiRNAs, a small non-coding RNAs are involved in the regulation of multiple biological process, including cell proliferation and inflammation response in different pathologies, are released locally and systemically by a variety of shuttles (exosome, lipoproteins, protein) that likely affect the efficacy of their biological effects^[34]. Transfer and modulation of gene expression by diet-derived microRNAs (miRs) in mammals might be involved in this communication. Circulating miRs might be active messengers eliciting a systemic response as well as non-specific “by-products” of cell activity and even cell death. miRs can exert two opposite roles, activating as well as inhibiting inflammatory pathways. Supported by a “Pubmed” search validated inflammatory-miRs were to be miR146a, miR-155, and miR-21^[35]. On the whole, it seems clear that management of gut microbiota and chronic inflammation may be the most important factors underlining age-related chronic health conditions.

miR146a up-regulation may reduce the inflammatory cascade

Treatment of chondrocytes with 6-mer hyaluronan (HA) showed up-regulation in inflammation parameters such as TLR-4, and CD44 receptors activation, IL-6, IL-1β and MMP-13 mRNA expression and proteins production, as well as NF-κB activation. Among several known regulatory miRNA, miR146a was shown to be involved in proinflammatory processes. Avenoso *et al*^[36] investigated the levels of miR146a and its correlation with inflammatory mediators in an experimental model of 6-mer HA-induced inflammatory response in human cultured chondrocytes. The authors concluded that up-regulation of miR146a occurred in 6-mer HA-induced inflammation response may reduce the inflammatory cascade by modulating TLR-4 and NF-κB activation.

The role of miR-21 in inflammatory osteoclastogenesis inhibition by aloin

The pro-osteoclastogenic nature of miR-21 makes it a potential candidate as a therapeutic target to treat bone disorders. Aloin was effective in promoting osteoblastogenesis and inhibiting osteoclastogenesis. Madhyastha *et al*^[37] showed the role of miR-21 in aloin’s inhibitory effect on osteoclast differentiation. Aloin effectively suppressed receptor activation of nuclear NF-κB ligand miR-21 expression via repression of NF-κB activation. MiR-21 suppression resulted in upregulation of osteoclast suppressor programmed cell death protein 4, and downregulation of osteoclast marker cathepsin K. The authors exhibited that miR-21 was pivotal to aloin’s inhibitory effect on osteoclastogenesis.

SUMMARY

In the review paper, we covered putative role of aloe ingredients in aging and age-related disease by focusing on microbiota and senoinflammatory process. We further elaborated on the regulation of intestinal homeostasis by butyrate, prevention of leaky gut by aloin and butyrate, and putative roles of aloe vera juice ingestion

for restoring the gut integrity which could be possibly included in reducing changes in chronic inflammation, gut microbiome, and leaky gut: intestinal permeability structure in aging and age-related diseases. Present review article brings together in a comprehensive manner under the main theme of modification of gut microbiota, because inflammatory process, microbiota, and gut integrity are all inter-dependent by sharing common or similar mechanistic processes. In this review, we described putative roles of aloe ingredients and fermented butyrate based on their ability to attenuate the chronic senoinflammatory process of aging and age-related diseases.

REFERENCE

- Ikeno Y, Hubbard GB, Lee S, Yu BP, Herlithy JT. The influence of long-term aloe vera ingestion on age-related disease in male Fischer 344 rats *Phytotherapy Res.* 2002; **16**: 712-718 [DOI: 10.1002/ptr.1022]
- A Yagi and BP Yu. Prophylactic Aloe components on autoimmune diseases: Barbaloin, aloe-emodin, emodin, and fermented butyrate *J. of GHR* 2018; **7(2)**: 2537-2541 [DOI: 10.17554/j.issn.2224-3992.2018.07.762]
- Chung HY, Kim DH, Lee EK, Chung KW, Chung S, Lee B, Seo AY, Chung JH, Jung YS, Im E, Lee J, Kim ND, Choi YJ, Im DS, Yu BP. Redefining chronic inflammation in aging and age-related diseases: Proposal of the senoinflammation concept *Aging and Disease* 2019; **10 (2)**: 367-382 [PMID: 31011483]; [DOI: 10.14336/AD.2018.0324]
- vel Szic KS, Declerck K, Vidakovic M, Vanden Berghe W. From inflammaging to healthy aging by dietary life style choices: Is epigenetics the key to personalized nutrition? *Clinical Epigenetics* 2015; **7**: 33 [DOI: 10.1186/s13148-015-0068-2]
- Shintouo CN, Mets T, Beckwee D, Bautmans I, Ghogomu SM, Souopgui J, Leemans L, Meriki HD, Njemini R. Is inflammaging influenced by the microbiota in the aged gut? A systematic review *Experimental Gerontology* 2020; **141**: 111079 [DOI: 10.1016/j.exger.2020.111079]
- Salazar N, Arbolea S, Fernandez-Navarro T, de Los Reyes-Gavilan CG, Gonzalez S, Gueimonde M. Age-associated changes in gut microbiota and dietary components related with the immune system in adulthood and old age: A cross-sectional study *Nutrients.* 2019; **11(8)**: 1765 [PMID: 31370376]; [DOI: 10.3390/nu.11081765]
- Ragonnaud E and Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people *Immunity & Ageing* 2021; **18(2)**: 2 [DOI: 10.1186/s12979-020-00213-w]
- A Yagi, A Kabbash, LA Al-Madboly. 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]
- LA Al-Madboly, A Kabbash, AM Yassin, A Yagi. Dietary cancer prevention with butyrate fermented by Aloe vera gel endophytic microbiota *J. of GHR* 2017 **6(2)**: 2312-2317 [DOI: 10.17554/j.issn.2224-3992.2017.06.698]
- Okamura N, Asai N, Yagi A. High-performance liquid chromatographic determination of phenolic compounds in Aloe species *J. of Chromatography A.* 1996; **746**: 225-231
- A Yagi and BP Yu. Epigenetic roles of microbiota and Aloe vera in health and disease *J. of GHR* 2019; **8(3)**: 2871-2878 [DOI: 10.17554/j.issn.2224-3992.2019.08.830]
- A Yagi and BP Yu. Fermented butyrate of *Aloe vera* and *A. arborescens* by endophytic bacteria: Its prophylactic action on brain insulin resistance *J. of GHR* 2019; **8(4)**: 2896-2901 [DOI: 10.17554/j.issn.2224-3992.2018.08.836]
- A Yagi and BP Yu. 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]
- A Yagi, T Kambara, N Morinobu. Inhibition of mushroom-tyrosinase by aloe extract *Planta Med.* 1987; **53(6)**: 515-517. [PMID: 17269093]; [DOI: 10.1055/s-2006-962798]
- Jones K, Hughes J, Hong M, Jia Q, Orndorff S. Modulation of melanogenesis by aloesin: A competitive inhibition of tyrosinase *Pigment Cell Res.* 2002; **15**: 335-340
- Wahedi HM, Jeong M, Chae JK, Do SG, Yoon H, Kim SY. Aloesin from Aloe vera accelerates skin wound healing by modulating MAPK/Rho and Smad signaling pathway in vitro and in vivo. *Phytomedicine* 2017; **28(15)**: 19-26 [DOI: 10.1016/j.phymed.2017.02.005]
- Park MY, Kwon HJ, Sung MK. Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages *Biosci Biotechnol Biochem.* 2009; **73(4)**: 828-832 [PMID: 19352036]; [DOI: 10.1271/bbb.80714]
- Cho S, Lee S, Lee MJ, Lee DH, Won CH, Kim SH, Chung JH. Dietary Aloe vera supplementation improves facial wrinkles and elasticity and it increases the type1 procollagen gene expression in human skin in vivo. *Ann Dermatol.* (Seoul) 2009; **21**: 6-11
- Zhong J, Wang F, Wang Z, Shen C, Zheng Y, Ma F, Zhu T, Chen L, Tang Q, Zhu J. Aloin attenuates cognitive impairment and inflammation induced by D-galactose via down-regulating ERK, p38 and NFκB signaling pathway. *Int. Immunopharmacology* 2019; **72**: 48-54 [DOI: 10.1016/j.intimp.2019.03.050]
- Gokulan K, Kolluru P, Cerniglia CE, Khare S. Dose-dependent effects of aloin on the intestinal bacterial community structure, short chain fatty acids metabolism and intestinal epithelial cell permeability *Front Microbiol.* 2019; **10**: 474 [PMID: 30972034]; [DOI: 10.3389/fmicb.2019.00474]
- Putri RR, Nugraha T, Christy S. Extraction of hyaluronic acid from Aloe vera *J. of Fun. Food and Nutraceuticals* 2020; **1(2)**: 95-102. [DOI: 10.33555/jffn.v1i2.33]
- Petrey AC, de la Motte C. Hyaluronan, a crucial regulator of inflammation *Front. Immunol.* 2014; **5**: 101 [DOI: 10.3389/fimmu.2014.00101]
- A Yagi 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]
- A Yagi and BP Yu. Immune modulation of aloe vera: Acemannan and gut microbiota modulator *J. of GHR* 2015; **4(8)**: 1707-1721 [DOI: 10.17554/j.issn.2234-3992.2015.04.525]
- A Yagi and BP Yu. Immune modulation by microbiota sources: Effects of aloe vera gel and butyrate *J. of GHR* 2018; **7(5)**: 2681-2689 [DOI: 10.17554/j.issn.2224-3992.2018.07.791]
- Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, Korecka A, Bakocevic N, Ng LG, Kundu P, Gulvas B, Haldin C, Hultenby K, Nilsson H, Hebert H, Volpe BT, Diamond B, Pettersso S. The gut microbiota influence blood-brain barrier permeability in mice *Sci Transl Med.* 2014; **6 (263)**: 263re158 [PMID: 25411471]; [DOI: 10.1126/scitranslmed.3009759]
- Nusrat A, Turner JR, Madra JL. Molecular physiology and pathophysiology of tight junction IV. Regulation of tight junctions by extracellular stimuli: nutrients, cytokines, and immune cells *Am J Physiol Gastrointest Liver Physiol.* 2000; **279(5)**: G851-7. [PMID: 11052980]; [DOI: 10.1152/ajpgi.2000.279.5.G851]
- MacFie J. Enteral versus parenteral nutrition: The significance of bacterial translocation and gut-barrier function *Nutrition* 2000; **16**: 606-611. [PMID: 10906570]; [DOI: 10.1016/s0899-9007(00)249-5]
- Kim HW, Hang JH, Shin E, Shim KS, Lee CJ, Yoon YS, Oh SH. Processed aloe vera gel attenuates non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal injury by enhancing mucin expression *Food and Function* 2019; **9**: 06 [DOI: 10.1039/c9fo01307e]
- Pretorius E, Willers C, Hamman J, Steyn JD. Gastrointestinal region specific insulin permeation enhancement by aloe vera gel *Drug Delivery Letters* 2020; **10(2)**: 117-122 [DOI: 10.2174/22103

- 03109666191022153551]
31. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers *The J. of Nutrition* 2009; **139**(9): 1619-1625 [DOI: 10.3945/jn.109.104638]
 32. Wang S, Lv D, Jiang S, Jiang J, Liang M, Hou F. Quantitative reduction in short chain fatty acids, especially butyrate, contributes to the progression of chronic kidney disease *Clin Sci. (London)* 2019; **133**(17): 1857-1870 [DOI: 10.1042/CS2019017]
 33. Wang RX, Lee JS, Campbell EL, Colgan SP. Microbiota-derived butyrate dynamically regulates intestinal homeostasis through regulation of actin-associated protein synaptopodin *PNAS* 2020; **117**(21): 11648-11657 [DOI: /10.1073/pnas.1917597117]
 34. Olivieri F, Albertini C, Orciani M, Ceka A, Cricca M, Procopio AD, Bonafe M. DNA damage response and senescence: shuttle inflamm-miRNAs on the stage of inflamm-aging *Oncotarget*. 2015; **6**(34): 35509-21 [PMID: 26431329]; [DOI: 10.18632/oncotarget.5899]
 35. Teodori L, Petrigiani I, Giuliani A, Prattichizzo F, Gurau F, Maccacchione G, Olivieri F, Coppari S, Albetini MC. Inflamm-aging microRNAs may integrate signals from food and gut microbiota by modulating common signaling pathways *Mech Aging Dev*. 2019; **182**: 111127; [PMID: 31401225]; [DOI: 10.1016/j.mad.2019.111127]
 36. Avenoso A, D'Ascola A, Scuruchi M, Mandraffino G, Campo S, Campo GM. MiR146a up-regulation is involved in small HA oligosaccharides-induced pro-inflammatory response in human chondrocytes *Biochimica et Biophysica Acta- General Subjects* 2021; **1865** (1): 129731 [DOI: 10.1016/j.bbagen.2020.129731]
 37. Madhyastha R, Madhyastha H, Pengiam Y, Nurrahmah QI, Nakajima Y, Maruyama M. The pivotal role of microRNA-21 inhibition by anthracycline glycoside aloin *J. Nat. Med.* 2019; **73**: 59-66 [PMID: 30116953]; [DOI: 10.1007/s11418-018-1237-3]