

Possible Prophylaxes of Aloe Vera Gel to micRNA Regulation and Questionnaire of Aloe Supplementation to Health Maintenance

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Abstract

In the review we discussed recent studies of aloe vera gel to micRNA regulation and micRNA involved in communication between macrophages and natural killer cells. Furthermore possible prophylaxis of a dietary supplement during four months containing spray-dried powder of aloe vera gel, ginger, cloud ear mushroom etc., was demonstrated by questionnaire included 14 points to 56 volunteer subjects suffering for diabetes, hypertension, constipation, and so on. Aloe vera supplementation significantly decreased HbA1C level in diabetes-like old-aged volunteers, and improved body temperature in *hie-sho-female*, prevented cold fever, and maintained health in adult subjects.

Keywords: Aloe Polysaccharide; micRNA Regulation; Aloe Vera Supplementation; Questionnaire

Introduction

The dietary supplement health and education act of 1994 is a state of United State Federal Legislation which defines and regulates dietary supplements (DS). The office of DS was established at National Institute of Health (NIH) in November 1995 and is to explore more fully the potential role of DS in maintaining health and chronic diseases and conducts and coordinates scientific research within NIH relating to DS. Since then garlic, ginger and aloe vera gel are main DS in world. In previous papers putative prophylaxes of aloe vera gel for age-related diseases have been interviewed [1,2].

In the designer foods project at the National Cancer Institute on 1991, the potential value of the twenty million dollar program, was underscored by recent findings in several countries showing that people who eat the most valuable and fruits such as garlic, ginger, ginseng, licorice and cabbage have the lower death rate from many common types of cancer, including those of lung, breast, prostate and colon. One of the designer foods ginger (*Zingiber officinale*) extract contains palatable smell and has a hyper-thermic effect on the peripheral extremities in women suffering from mild cold sensitivity, even if at a low dose of gingerols, a mixture of the components in ginger extract. Therefore, this beverage may help to improve cold sensitivity of the subjects suffering from *hie-sho* in traditional medicine patterns [3].

Based on the improvement of nutrients in food, Standard Tables of Food Composition in Japan, 2015 (Seventh revised version; STFC) was published according to basic data bases recommended by the Food and Nutrition Paper of Food and Agriculture Organization of the United Nations [4]. In STFC Aloe leaves (food number: 06328) are classified in Section: Vegetables.

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A novel virus (COVID-19) was identified as one of the acute respiratory syndrome corona virus (SARSCOV-2) and emerged as a pandemic disease in Asia, European countries and United States in 2020. COVID-19 is a positive-sense single-stranded RNA [(+) ssRNA] virus. The COVID-19 main proteases play very important role in the propagation of the novel coronavirus. The novel drug was identified by Rathinavel, *et al.* [5] and well studies against the viral receptors by using the molecular docking technique were reported. Phytochemical 6-gingerol possesses excellent drug likeliness with zero violations and very good pharmacokinetic properties with the highest binding affinity range from -2.8764 KJ/mol to -15.7591KJ/mol with various COVID-19 vial protein targets. The study reveals that 6-gingerol from Ginger could act as a promising drug of choice to treat COVID-19.

Chandel, *et al.* [6] have applied a drug repurposing approach of computational methodology, depending on the synergy of molecular docking and virtual screening techniques, aimed to identify possible potent inhibitors against COVID-19 from FDA approved antiviral compounds and from the library of active phytochemicals. On the basis of recently resolved COVID-19 main protease crystal structure, the library of 100 FDA approved antiviral compounds and 1000 active components of Indian Medicinal Plants extracted for screening against COVID-19 main protease. Nelfinavir (an antiretroviral drug used in the treatment of HIV) exhibited highest binding energy -8.4 kcal/mol and aloe-emodin (-7.4 kcal/mol) showed good binding affinity and best ADME properties. These compounds can be used as potential inhibitors against COVID-19 main protease, which could be helpful in inhibiting the propagation of the novel COVID-19.

In our previous papers we identified bradykinin degrading carboxyl peptidase N- and P-like glycoprotein in *Aloe saponaria* [7] and *A. arborescens* [8] and Bautista-Perez, *et al.* [9] fractionated anti-bradykinin activity of *A. vera* gel. Bradykinin is a physiologically and pharmacologically active peptide composed of nine amino acids. Angiotensin converting enzyme (ACE) inhibitors increase bradykinin levels by inhibiting degradation, thereby increasing its blood pressure lowering effect. ACE2 is known to play a role in maintaining blood pressure throughout the body, but it also has another function. ACE2 keeps the substance bradykinin under control, which makes blood vessels leak. Van de Veerdonk, *et al.* [10] proposed hypothesis that with COVID-19 infections ACE2 receptors disappear from the lung cells, giving bradykinin free rein in causing the small blood vessels to leak massively at the site of infection. A bradykinin-dependent local lung angioedema via bradykinin receptor B1 and B2 is an important feature of COVID-19, resulting in a very high number of ICU admissions. The long lasting vascular leakage and inflammation of the blood vessels will trigger the coagulation cascade leading to thrombosis and eventual scarring of the lungs.

An active glycoprotein fraction (verectin) isolated from aloe vera gel showed a radical scavenging activity against superoxide anion generated by the xanthine-xanthine oxidase system as well as inhibition of cyclooxygenase (COX)-2 and reduction of thromboxane (Tx) A2 synthase level *in vitro* [11]. Aloe also contains a bradykinin-kinase, which is active in inhibiting inflammation in the wound bed. Glycoprotein verectin seems to be involved in the initial vasoconstriction via cell proliferation and shows wound healing activity such as inhibition of Tx A2 and COX-2. Thus, verectin could be involved in the wound-healing effect via cell proliferation and migration.

In our previous paper [12] we described that microbe-induced butyrate regulates host gene expressions involved in intestinal homeostasis as well as carcinogenesis through modulation of microRNAs and activation of macrophages and vaccine adjuvant by aloe polysaccharide, acemannan, may originate in butyrate fermented by endophytic bacteria in aloe vera gel. Yagi, *et al.* [13,14] reported that diet metabolism and immunomodulatory activity linked to both to each other, allowing mammals to adapt to diverse changes in their intestinal gut environments. The obesity as a primary source of disease brings about metabolic dysfunction followed by inflammatory insulin resistance. The metabolites of aloe poly-mannose moiety, a manno-oligosaccharide and short chain fatty acids, such as butyric acid synergistically modulated insulin sensitivity on tissues, suggesting that putative efficacy of aloe vera gel metabolite in long-term ingestion to insulin sensitivity. Several host microRNAs (miRNAs) which are small non-coding RNA that are commonly present in normal cells, have been found to interact with the intestinal microbial community. Microbe-derived butyrate regulates host gene expression involved in intestinal homeostasis as well as carcinogenesis through modulation of miRNAs, and the activation of macrophages and vaccine adju-

vant by aloe polysaccharide (acemannan) may originate in butyrate fermented by endophytic bacteria in Aloe vera gel [15]. Furthermore, we described the effects of a dietary supplementation of aloe vera juice with L-arginine [16] to chronic fatigue syndrome and CoQ10 to enhance muscle performance [17] in which aloe vera juice plays a significant role of an adjuvant.

In chronic kidney disease (CKD), the accumulation of gut-microbial derived uremic toxins, such as indoxyl- and p-cresol sulfate accelerates the progression of CKD and mortality. Gut microbiota has been recognized as an important endogenous organ. The interest in butyrate producing endophytic bacteria in aloe vera gel has recently increased, and we discussed to CKD and uremic toxins in previous papers [18,19].

Owing to the laxative properties, the presence of aloin in the aloe preparations intended for use in foods is controlled and limited. International Aloe Science Council has established a quality standard for their certification program of not more than 10 ppm aloin A+B for all oral consumption.

The pivotal role of miRNA by anthrone C-glycoside, aloin (barbaloin)

MicRNA-21 suppression in osteoclastogenesis by aloin

MicroRNAs (MiRNAs) are emerging as key players in bone remodeling, modulating the functions of both osteoblasts and osteoclasts. Among them, micR-21 is highly expressed in osteoclast precursors and is known to regulate genesis, differentiation, and apoptosis of osteoclasts. The pro-osteoclastogenic nature of micR-21 makes it a potential candidate as a therapeutic target to treat bone disorders.

Madhyastha, *et al.* [20] investigated the role of micR-21 in aloin's inhibitory effect on osteoclast differentiation. Aloin effectively suppressed receptor activator of nuclear factor kappa-B (NFκB) ligand (RankL)-induced micR-21 expression via repression of NFκB activation. MicR-21 suppression resulted in upregulation of osteoclast suppressor programmed cell death protein 4, and downregulation of osteoclast marker cathepsin K.

MiRNA regulation of the glycome

Glycosylation is a sophisticated informational system that controls specific biological functions at both the cellular and organismal level. Dysregulation of glycosylation may underlie some of the most complex and common diseases of the modern era. In the past several years, miRNA have come to the forefront as critical regulators of the glycome. Glycome is the entire complement of sugars, whether free or present in more complex molecules, of an organism. Glycomics, analogous to genomics and proteomics, is "the systematic study of all glycan structures of a given cell type or organism" and is a subset of glycol-biology. The spectrum of all glycan structures -glycome- is immense. In human, its size is orders of magnitude greater than the number of proteins that are encoded by the genome, one percent of which encodes proteins that make, modify, localize or bind sugar chains, which are known as glycan [21].

Mapping posttranscriptional regulation of the human glycome

Integrating the glycomic dataset with miRNA data, Agrawal, *et al.* [22] map miRNA regulations onto genes in glycan biosynthetic pathways (glycogenesis) that generate the observed glycan structures. The authors validate three of the predicated miRNA/glycogen regulatory networks: high mannose, fucose, and terminal β-galactNAc, identifying miRNA regulation that would not have been observed by traditional bio-informative methods. The works reveal critical nodes in the global glycosylation network accessible to miRNA regulation, providing a bridge between miRNA-mediated control of cell phenotype and the glycome.

Insights into miRNA regulation of the human glycome

Kasper, *et al.* [23] highlighted that miRNA are an underappreciated regulator of glycosylation, key glycosylation enzymes are highly regulated by miRNA and redundant glycosylation enzymes are non-redundant in miRNA regulation.

Cytoprotective effects of galact-oligosaccharides on colon epithelial cells via upregulating miR-19b

Sun., *et al.* [24] investigated six colitis-associated miRNAs can be altered by galact-oligosaccharides which protect FHC cells against LPS induced injury via miRNA-19b. Galact-oligosaccharides attenuate *Helicobacter hepaticus* induced colitis via miR-19b.

Aloe lectins in Aloe vera and *A. arborescens*

MicroRNAs (MiRNAs), small, non-coding endogenous RNAs, ~22 nucleotides in length, have been well characterized to play essential roles in regulation of the autophagy process in cancer. How these miRNAs regulate autophagic pathways in plant lectin-induced cancer cells still remains an enigma.

Fu., *et al.* [25] computationally constructed the human autophagic protein-protein interaction network, and further modified this network into a plant lectin-induced network. The results demonstrated that network-based identification of microRNAs modulate autophagic pathways in plant lectin-treated cancer cells, which may shed new light on the discovery of plant lectins as potent autophagic inducers, for cancer drug discovery. Alectin A and B were isolated from *A. arborescens* by Suzuki., *et al.* [26], and alectin I and II was isolated from *A. vera* by Akev group [27-29]. Although lectin-like activity of the glycoprotein in Aloe vera leaf gel was not examined, verectin was described as lectin because it promoted cell growth and resembled to alectin of *A. arborescens* in biological properties and molecular size by El-Shemy., *et al* [30]. Active principle of N-terminal octapeptide derived from 14 KD glycoprotein, verectin, exhibited significant prolongation of the life span of tumor-transplanted animals.

MiRNAs involved in communication between macrophages and tumor cells

The role of miRNAs in immune cell development, immune cell activation and tumor immunity focusing on macrophages and natural killer cells

Macrophages and natural killer (NK) cells are crucial components of the stromal compartment and display either pro- or anti-tumor properties, depending on the expression of key regulators. MiRNAs are emerging as such regulators. They affect several immune cell functions closely related to tumor evasion of the immune system. Xu., *et al.* [31] discussed the role of miRNAs in the differentiation, maturation, and activation of immune cells as well as tumor immunity, focusing partially on macrophages and NK cells.

The biological effects of edible plant derived exosome-like nanoparticles on mammalian cells

Mu., *et al.* [32] investigated that the edible plant derived exosome-like nanoparticles (EPDENs) contain proteins, lipids, mRNA, miRNA, and glycol-conjugates. Exosomes are extracellular vesicles that have the same topology as the cell and are rich in selected potential vehicle for bioactive compounds. EPDENs were taken up by intestinal macrophages and stem cells. The results generated from EPDEN-transfected macrophages indicated that ginger EPDENs preferentially induce the expression of the anti-oxidation gene, hemeoxygenase-1 and the anti-inflammatory cytokine, IL-10; whereas grapefruit, ginger, and carrot EPDENs promote activation of nuclear factor like. Analysis of the intestines of canonical Wnt-reporter mice revealed that the number of β -galactosidase intestinal crypts are increased, suggesting that EPDEN treatment of mice leads to Wnt-mediated activation of the TCF4 transcription machinery in the crypts. These data suggest a role for EPDEN-mediated interspecies communication by inducing expression of genes for anti-inflammation cytokines, anti-oxidation, and activation of Wnt signaling, which are crucial for maintaining intestinal homeostasis. Zhang., *et al.* [33] characterized a specific population of nanoparticles derived from edible ginger (GDNPs 2) and demonstrated their efficient colon targeting following oral administration. GDNPs 2 had an average size of ~230 nm and exhibited a negative zeta potential. These nanoparticles contained high levels of lipids, a few protein, ~125 micRNAs and large amounts of ginger bioactive constituents.

Butyrate, a well-known epigenetic HDAC inhibitor, was shown to induce cell cycle arrest, differentiation, miRNA expression, and apoptosis in colorectal cancer. In an earlier paper [34] we discussed aloe vera fermentation as a tumor-suppressive process generating microbial-derived butyrate. Ho., *et al.* [35] investigated the effect of HDAC3 targeting in bone marrow (BM) stromal cells (BMSC). The au-

thors identified both quantitative and qualitative changes in exosomes and exosomal miRNA, as well as inhibition of IL-6 trans-signaling, as molecular mechanisms mediating anti-multiple myeloma (MM) activity. Exosomes derived from HDAC3 knock down (KD) BMSC show downregulation of pro-survival miRNAs: miR380, miR382---. These data indicate that HDAC3 KD in HS-5 cells leads to downregulation of pro-survival miRNAs in exosomes obtained from BMSC-MM co-culture systems.

Bohler H and Zhang HG., used ginger or aloe to produce exosomes for treating patients diagnosed with polycystic ovary syndrome, expecting it to mitigate insulin resistance and chronic inflammation. They proposed the project: Plant exosomes and patients diagnosed with polycystic ovary syndrome on May 2019. The purpose of this study is to see if substances contained in ginger or aloe plants, called exosome, will treat and improve the condition polycystic ovary syndrome; Project number: NCT03493984.

Naturally occurring exosome-like extracellular vesicles play the role as potential delivery vehicle of biomarker. The development of exosomes may be an alternative candidate for treating diseases of un-stratified fields, such as cancer and inflammatory disease.

Anti-hypoglycemic and anti-fibrotic effects of aloe high molecular weight fractions

Anti-hypoglycemic effect of aloe high molecular weight fraction (AHM) on type2 diabetic patients

AHM produced significant decrease in blood glucose level sustained for 6 weeks of the start of the study. Treatment of diabetic patients with AHM may relief vascular complications probably via activation of immune-system [36].

Anti-fibrotic effect of aloe heigh molecular weight (AHM) in viral infection-induced hepatic periportal fibrosis

Oral administration with AHM treated with 0.15 g/d AHM for consecutive weeks. The patients were processed to 40 patients with liver fibrosis and were investigated before and after treatment with serum activity of AST, ALT, ALP, HA, TGF- β and MMP-2 were determined. The reduced GSH and MDA levels in liver were assayed and the expression of hepatic α -smooth muscle actin was identified by immunohistochemistry. Oral supplementation with AHM could be helpful in alleviating the fibrosis and inflammation of hepatic fibrosis patients [37].

Questionnaire including 14 points regarding health maintenance

We will discuss possible prophylaxes of aloe vera gel supplementation and questionnaire included 14 points regarding health conditions under the agreement of administration of principle of Helsinki declaration. Table 1 demonstrated the personal experiences on administration of aloe vera gel supplementation including ginger and cloud ear mushroom etc.

Materials and Methods

Cultivation of aloe vera in the field of Aloeland incorporation

There is a scarcity of information about the agronomic management of Aloe vera cultivation concerning for the effect of water availability with the establishment and gel production. Based on more than forty years Aloe vera cultivation in the field of Aloeland Inc., the effect of different condition on the growth efficiency for the production of leave biomass and gel was established as follows: basically no irrigation in all season; cultivation in the open-green house from May to November, and in the closed-green house from end of Nov. to next year April. The edapho-climatic condition based on atmospheric evaporative demand and soil water dynamics are seemed to be well maintained on the field of Aloeland Inc., located at Makinohara city bordered by Suruga Bay on the Pacific Ocean in Japan.

Aloe supplementation

Aloe vera gel is scratched out from the leaves and well washed with running water. Content of barbaloin in the gel was less than 0.5 ppm by HPLC analysis by Japan Food Research Laboratories. After drying in room temperature, the thick gel pasty was spray-dried without dextrin yielding natural aloe dried powders.

Aloe supplementation (AS) is composed of following dried powders: aloe vera gel, ginger, cloud ear mushroom, loquat leaves, cocoa nut and see weed etc.

Activity of radioactive cesium 134, 137 in AS was determined by Seikan Kensa Center Inc. Shizuoka-ken, according to Examination of Radioactive Substance in Foods. Radioactive cesium content was less than 8.8 Bq/kg.

Subjects ingested the solution of AS 1.5g in hot water ~1000 ml, 3 times a day for 4 months from February to June 2020.

Cloud ear mushroom

Wood ear mushroom (black fungus; *Auricularia auricular-judae*) contains β -glucans and is a great source of vitamin D, which contributes to the normal function of the immune system [38]. The aloe supplement contains natural grown wood ear mushroom harvested in Hitoyoshi City, Kumamoto, Japan.

Ginger

Ginger stimulates the system, warm the digestion and improve nutrient assimilation, and a specific remedy for hay fever and colds. Ginger powder certificated by Japanese Agricultural Standard was used in AS.

Response of aloe vera supplementation ingestion

The questionnaire assessment of volunteer 56 subjects of 37 male, 12 female; age-range from 40th to 80th old; recovery ration; 93%, in single respondent from the total 49 subjects; 7 subjects were excluded because of preliminary ingestion of aloe supplement and health food; term of the assessment was carried out during Feb. 6 to June 14, 2020. Questionnaire evaluation was based on the following scheme: before or after ingesting health conditioning. The questionnaire included 14 points regarding to diabetes, blood circulation, constipation, fatigue, and health conditions.

Results

It is well-know that ginger stimulates the system and digestion in warm and improves the nutrient assimilation as a specific herb for hay fever and cold. Cloud ear mushroom contains β -glucan and vitamin D, which contributes to the normal function of the immune system.

Present article exhibits that aloe vera supplementation in dry-powders including aloe vera gel, ginger, cloud ear mushroom, etc. may reduce blood sugar level in diabetic subjects and improve cold sensitivity in *hie-sho* subjects [3]. Type 2 diabetes mellitus is one of the primary threats to human health due to its increasing prevalence, chronic course and disabling complications.

In our earlier report we demonstrated that pre-clinical treatment of diabetic patients with aloe high molecular weight fractions (aloe polysaccharides) as an adjuvant may relief vascular complications via activation of immune system. Aloe polysaccharides exhibited a significant hypoglycemic effect and it can lower not only the glucose but also the triglycerides level which are often high in diabetic patients with no hepato- and nephrotoxicity [36]. Furthermore, we investigated the anti-oxidative and anti-fibrotic effects of aloe vera in patients with liver fibrosis. Oral supplementation with aloe vera high molecular weight fractions could be helpful in alleviating the fibrosis and inflammation of hepatic fibrosis patients [37].

The questionnaire included 14 points regarding to the health conditions and the evaluation was based on clinical comparison between before and after situations. There was no adverse effect from aloe vera supplementation (AS) ingestion through four months trial period.

Table 1 demonstrated the noteworthy information for putative prophylaxes of AS to diabetic, hypertensive, hay fever, and constipation conditions. HbA1C value calculated for volunteer subjects showed a significant reduction by 5% compared to before treatment ($P \leq 0.02$).

Questionnaire following to	Positive efficacy following to	Single responses (%)
1. Do you have any of chronic fatigue?	Condition lasting more than 6 months in which a person feels tired most of the time.	Much better: 39 No change: 61
2. Do you have any of diabetes trouble?	Breath, urinary, walking and sleeping. A1C value? A1C: before, 7.44, after 7.09. t = Test; P ≤ 0.02.	Slightly decrease: 57 No change: 10 Slightly increase: 33
3. Do you have any of hypertension?	Sleeping, breathing, vision. Systolic blood pressure?	Slightly decrease: 24 No change: 74 Slightly increase: 2
4. Do you have any of hay fever?	Seasonal hay fever, pollen hay fever, hay fever asthma	Slightly decrease: 31 No change: 69
5. Constipation management?	Chronic, intractable or elderly constipation	Improving :14 No change: 86
6. Do you have any of weight trouble?	Weight gain, lose or no change	Slightly decrease: 24 No change: 76
7. How body temperature?	Normal, high or low body temperature	Slightly high, 35.8~36.5°C: 55 No change: 45
8. How serum neutral cholesterol level?	LDL/HDL > 2.0; Early sign of arteriosclerosis	Ratio ≥2.5: 27 Ratio 1.6~2.4:72 Ratio < 1.5: 1
9. How foot swelling?	Swelling weak, mild or strain	Improvement: 16 No change: 84
10. Do you have any of fatigue and languid syndrome?	Tiredness, weary or fatigue	Improvement: 39 No change: 61
11. Do you have any of leg cramp in the calf muscle?	Relax, tense or heavy symptom	Improvement: 32 No change: 68
12. Do you have any of opportunity to get fever in cold season?	Normal range, high range, or low range	Improvement: 55 No change: 45
13. How urinary output of urinary frequency and amount?	Normal, high, or low account/ amount	High account: 33 High amount: 20 No change: 47
14. Do you have any trouble of alcohol detoxification, withdrawal seizures?	Detoxification categories in mild, modulate or not be hang-over	Not be hang-over: 14 No change: 86

Table 1: Response of aloe vera supplementation ingestion to before and after health conditions.

Discussion

In our earlier study the base peak sequence of the internally transcribed spacer (ITS) 1 region of rDNA was adopted as a molecular marker for differentiating Aloe vera plants from geographically distributed and clonally regenerated Aloe vera plants in Fukuyama, Hiroshima-Japan, USA (State of Texas) and Tanta in Egypt. The results revealed the presence of two types of nucleotide sequence, 252 and 254 bps. Based on the findings in the ITS region, Aloe vera having 252 and 254 bps clearly showed a stable sequence similarity, suggesting high conservation of the base peak sequence in the ITS region. It was suggested that the base peak substitution in the ITS 1 region may arise from the different nutritional and environmental factors in cultivation and plant growth stages [39].

The effect of water availability for aloe leaves establishment and production was to evaluate the effect of different irrigation rates on the growth and efficiency of water usage for the production of leaves biomass and gel. Silva, *et al.* [40] reported that the requirement,

based on the interaction among the metabolic pathway, atmospheric evaporative demand and soil water dynamics, was 15% of the reference evapotranspiration. Furthermore, the authors investigated the synthesis and the protective role of neo-fructans under extreme water deficient in northern Chile [41,42].

In the present study aloe supplementation (1.5g) with high viscosity and solubility in hot water 500 ml/day, was administered 49 subjects for four months.

Questionnaire assessment of volunteer 49 subjects of male 37 and female 12 and age-range from 40th to 80th years old was carried out. Recovery ration: 93% and 7 subjects were excluded because of preliminary ingestion of health food.

Questionnaire evaluation was based on the following scheme: 1: Slightly bad, 2: No change, 3: Much better and improvement. Table 1 demonstrated the noteworthy beneficial information of aloe vera supplementation showing non-radioactive cesium and non-aloin content.

Summary

In the previous paper we discussed the health-promoting potential of the balanced gut microbiota and health maintenance with long-term intake of aloe vera gel juice [15]. In the present paper we described how the microbiota modulate metabolic disease and MicRNA regulate the glycome.

Furthermore, the results of questionnaire demonstrated that aloe vera supplementation may have potential as putative prophylaxes to diabetes, *hie-sho*, hay fever, cold fever, hypertension, constipation and be hang-over subjects. HbA1C value calculated for volunteer subjects showed a significant reduction by 5% in after treatment compared to before treatment ($P \leq 0.02$) during four months ingestion of aloe vera supplementation.

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