

Possible Efficacy of aloe vera gel Metabolites in Long-Term Ingestion to Insulin Sensitivity

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ABSTRACT

Diet metabolism and immunomodulatory activity are linked to both to each other, allowing mammals to adapt to diverse changes in their intestinal gut surroundings. The obesity as a primary source of disease brings about metabolic dysfunction followed by inflammatory insulin resistance. The metabolites of aloe polymannose moiety, such as a mannoooligosaccharide and short chain fatty acids, synergistically modulated insulin sensitivity on tissues with combination of phenolics, such as aloesin, aloe emodin (a metabolite of barbaloin) and salicylate in aloe vera gel. The insulin levels and insulin activity in the central nerve system, such as hippocampus, are reduced in Alzheimer's disease (AD) and amnesic mild cognitive impairment (MCI). Restoring insulin levels to normal in the brain may provide therapeutic benefit to elderly subjects with AD and amnesic MCI. The effect of aloe polymannose multinutrients complex (APMC) on cognitive and immune functioning in AD showed the improvements in both clinical and physiological outcomes, though the several limitations of the current investigation were noted. APMC may offer an alternative opinion for persons with AD and amnesic MCI. Present review showed a possible putative efficacy of aloe vera gel metabolites in long-term ingestion to insulin sensitivity.

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Key words: Possible efficacy; aloe vera gel metabolites; Insulin sensitivity

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INTRODUCTION

Deficiency of insulin or the insensitivity of its receptors plays a key role in all forms of diabetes; type 1 and 2 diabetes, and plant ingredients showing hyper-glycemic activity were screened by using the platform of computer-aided drug designing (CADD). Through CADD, barbaloin in aloe vera was selected as one of candidate by using the diabetic inhibitor drug, glipizide. Pharmacokinetic studies of the compounds such as, barbaloins exhibited less toxicity on various levels of the body as a ligand^[1].

Thirteen natural products of plants was in silico analysed to predict the most likely effective artificial mixtures of 2-3 most effective natural products on leukemia cells from over 364 possible mixtures. Among natural products, the combinations of aloe emodin of barbaloins metabolite^[2], barbaloins, aloesin and salicin in aloe vera were predicted to be one of the effective combination for acute myeloid leukemia-related predicted binding proteins^[3]. These findings may indicate the potential functions attributing to drug synergism of phenolic ingredients in aloe vera.

In earlier preclinical studies, the potential aloe vera gel for treatments of viral infection-induced hepatic periportal fibrotic, type 2 diabetic, bed sores- and lichen planus-suffering patients, was sufficiently approved as an immunomodulator^[4]. And the efficacy of insulin was emphasized in wound healings from r-ray radiation-induced damages^[5]. The metabolites and immunomodulatory activity are linked both to each other allowing mammals to adopt to changes in their intestinal surroundings. Aloe polysaccharide having immunomodulatory as adjuvant synergistically exerted biological activity with phenolic ingredients in aloe vera gel.

The aim of present review is to express the possible efficacy of metabolites of aloe vera gel to insulin sensitivity or its receptors, excluding the study of alterations in intestinal microbiota composition correlated with the long-term aloe vera gel ingestion.

METABOLITES OF ALOE POLYSACCHARIDES

Mannooligosaccharide (MOS)

Prebiotics that are non-digestible food ingredients currently in use are mainly carbohydrates of low digestibility, such as polymannose in aloe vera gel and coffee seeds. Biodisposition of fluoresceinyl isothiocyanate (FITC)-labeled aloemannan (FITC-AM) with the homogenate from large intestine in mice was demonstrated, and FITC-AM was metabolized to two smaller molecules (FITC-9 and 12 x hexose in 6 hours incubation and FITC-2 x hexose in 24 hour incubation) by the large intestinal microflora in feces^[6].

Dietary MOS which was derived from coffee with a degree of polymerization distribution of 2-6 (DP 2-6), on the immune system of ovalbumin-sensitized mice was investigated and MOS treatment significantly reduced IL-10 production and tended to suppress ovalbumin-specific IgE in serum. These results suggested that dietary MOS may have an anti-allergic effect^[7]. Dietary products enhancing sustainable fibrolytic fermentation in the colon, such as mannose polysaccharides in aloe vera gel, would be beneficial for elderly, as the metabolites may increase MOS and short chain fatty acids levels^[8].

β -1,4-Mannobiose (MNB) exerted prebiotic activity and modulated mucosal gene expression in mice. The immune modulatory effect of MNB in healthy and endo-toxicemic mice and its role in TLR (Toll like receptor) 2- and 4-mediated macrophage activation was investigated and MNB modulated intestinal and systemic immune responses in healthy and endotoxemic mice and prevented LPS-induced immune suppression, stimulating innate immune mechanisms in vitro as a TLR 4 agonist^[9].

Clinical studies of coffee MOS showed that the consumption decreased body fat, suggesting that MOS consumption may be useful for weight management^[10].

Further study on a weight-loss diet including MOS enhanced adipose tissue loss in overweight men not women, suggesting a potential functional use of MSO for weight control and improvement in adipose tissue distribution^[11].

Short chain fatty acids (SCFAs)

SCFAs, such as acetate, propionate and butyrate, are metabolites formed by gut microbiota from complex dietary carbohydrates. Butyrate and acetate were reported to protect against diet-induced obesity without causing hypophagia, while propionate was shown to reduce food intake. The authors examined the effects of SCFAs administration in mice, and showed that butyrate, propionate, and acetate all protected against diet-induced obesity and insulin resistance. Butyrate and propionate but not acetate, induced gut hormones and reduced food intake. As free fatty acids receptor 3 (FFAR3) is the common receptor activated by butyrate and propionate, the authors examined these effects in FFAR3-deficient mice. The effects of butyrate and propionate on body weight and food intake were independent of FFAR3. In addition, FFAR3 played a minor role in butyrate stimulation of glucagon-like peptide-1, and is not required for butyrate- and propionate-dependent induction of glucagon-dependent insulinotropic peptide. FFAR3-deficient mice showed normal body weight and glucose homeostasis. Stimulation of gut hormones and food intake inhibition by butyrate and propionate may represent a novel mechanism by which gut microbiota regulates host metabolism^[12].

In humans, SCFAs are derived in large part from fermentation of carbohydrate and protein in the colon. By this process the host is able to salvage energy from foods that can not be processed normally in

the upper parts of the gastrointestinal tract. In humans, SCFAs are derived in large part from fermentation of carbohydrate and protein in the colon. By this process the host is able to salvage energy from foods that can not be processed normally in the upper parts of the gastrointestinal tract. In humans, SCFAs are a minor nutrient source. Recent studies have described multiple beneficial roles of SCFAs in the regulation of metabolism. Further interest in SCFAs has emerged due to the association of gut flora composition with obesity and other metabolic status. The recent identification of receptors specifically activated by SCFAs, such as FFAR2 and 3, was considered to be metabolically important. The studies examining the role of these receptors and their ligands, SCFAs, in metabolism are emerging^[13].

The relative or absolute deficiency of pancreatic β -cell mass function underlies the pathogenesis of diabetes. It is necessary to alleviate the metabolic stress and reduce the demand for insulin to decrease the effects of mutations affecting β cell expression. Butyrate is a natural nutrient existed in food and can be produced physiologically through the intestinal fermentation of fiber. Pregnancy and obesity model would be helpful for understanding how cell adapt to insulin resistance and how butyrate alleviate the metabolic impairment and protect pancreatic β -cell function in pregnant mice with obesity. C57BL/6J female mice were fed with high fat food (HF group, 40% energy from fat) displayed β -cell hyperplasia with a greater β -cell size and β -cell area in pancreas. Furthermore, the higher ratio of apoptosis and inflammatory response were found in HF group compared with high fat with sodium butyrate food (HSF group, 95% HF with 5 % butyrate) and control food (CF group, 14% energy from fat), while the proliferation rates of β -cell increased in HF group, but not in HSF or CF. Butyrate showed an obvious function of anti-obesity and can alleviate the metabolic stress, maintain the β -cell function and protect them from inflammatory response in pregnant obese mouse without obvious fetus toxicity^[14].

There are results suggesting that butyrate explains the association between the intestinal ecosystem and host metabolic health. Real-time PCR analysis and in-depth microbiome sequencing have revealed lower abundance of butyrate-producing bacteria in patients with T2D. Additionally, intervention with butyrate per se or modulation of the intestinal microbiota to increased growth of butyrate products have been associated with beneficial effects on insulin sensitivity both in mice and humans. The anti-inflammatory potential for butyrate is due to the enhancement of the intestinal barrier function that prevents the translocation of inflammatory molecules. Butyrate enhanced intestinal barrier function as it is the main nutrient for colonic epithelial cells and it regulates homeostasis in the colonic epithelium as well as the tight junction proteins and mucins. Thus, the authors concluded that butyrate, at least partly, provides a link between diet, intestinal microbiota and metabolic health^[15].

The gut microbiota affects nutrient acquisition and energy regulation of the host, and can influence the development of obesity, insulin resistance, and diabetes. The authors showed that the SCFAs receptor (GPR43) links the metabolic activity of the gut microbiota with host body energy homeostasis, and demonstrated that GPR43-dependent mice are obese on a normal diet, whereas mice overexpressing GPR43 specifically in adipose tissue remain lean even when fed a high-fat diet. Raised under germ-free conditions or after treatment with antibiotics, both types of mice have a normal phenotype. The authors further showed that SCFAs-mediate activation of GPR43 suppresses insulin signalling in adipocytes, which inhibits fat accumulation in adipose tissue and promotes the metabolism of unincorporated lipid and glucose in other tissues. The authors expressed that these findings establish GPR43 as a sensor for

excessive dietary energy, thereby controlling body energy utilization while maintaining metabolic homeostasis^[16].

A double-blind, placebo-controlled, crossover human intervention study was conducted. Volunteers were assigned, 3 g MOS and placebo coffee preparations to consume daily over a 3 weeks, followed by a 2 week washout period.

Faecal samples were collected, and microbial population characterized using fluorescence in situ hybridization. Short-chain and branched-chain fatty acid profiles were obtained by gas chromatography. All treatments led to significant lactobacilli increases (placebo, $p < 0.001$; 3 g, $p = 0.04$; 5 g, $p = 0.04$). The 3 g treatment led to a significant bifidobacteria increase ($p = 0.001$). Significantly less iso-valerate was found in faeces following 3 g MOS daily ($p = 0.05$). In conclusion, the 3 g dose of MOS led to a potentially beneficial shift in the faecal microbiota. MOS was therefore confirmed to be a prebiotic at 3 g dose. Significance and impact of the study showed that this study provides confirmation of a new novel prebiotic, that can be considered for incorporation into a wider variety of food products, to provide different selective and nutritional properties^[17].

METABOLITES OF POLYPHENOLICS

The systemic report was presented to review the evidence base supporting the use of salicylates for glucose level control in patients with type 2 diabetes and provide a comprehensive review of available information describing the potential role of salicylates and in particular, salsalate (a dimer of salicylic acid), for glucose control in type 2 diabetes prevention and treatment. All relevant English-language information on the pharmacology, efficacy, and safety of salicylates for glucose control related to insulin resistance or diabetes prevention were reviewed, including preclinical data, clinical trials, and case reports. In conclusion, salicylates, especially salsalate, appear to be promising treatment option for prevention or treatment of diabetes by lowering glucose levels^[18].

To determine the absorption and tissue distribution of the complex grape polyphenol mixture, ¹⁴C-labeled polyphenols were biosynthesized by grape cell suspension cultures, during co-incubation with radioisotopically labeled sucrose, and fractionized into polyphenolic subfractions. The pharmacokinetics and distribution of grape polyphenols into blood, brain, and peripheral interstitial fluid were determined by tracking the ¹⁴C label. The blood peak ¹⁴C concentration of the fractions ranged from 15 minutes to 4 hours. Absorption and tissue distribution varied greatly between fractions. Concentrations in interstitial fluid were lower than in blood. The amount of residual label in the brain at 24 hours ranged from 0.1% to 1.7% of the dose, depending on the fraction. ¹⁴C-labeled found in the brain tissue and brain microdialysate indicated that grape polyphenols or their metabolites are able to cross the blood-brain barrier. Using ¹⁴C-label plant polyphenols it is possible to track the compounds or their metabolic products into any tissue and determine distribution patterns in spite of low concentrations. The author's observations indicated that some grape-derived polyphenolics do reach the brain, which suggests their potential value for applications in neurodegenerative disorders^[19].

The authors showed that supplementation with pure anthocyanins or pure flavanols for 6 weeks, at levels similar to that found in blueberry (2% w/w), resulted in an enhancement of spatial memory in 18 month old rats. Pure flavanols and pure anthocyanins were observed to induce significant improvements in spatial working memory ($p = 0.002$ and $p = 0.006$, respectively), to a similar extent to that following blueberry supplementation ($p = 0.002$). These behavioral changes were paralleled by increases in hippocampal

brain-derived neurotrophic factor (BDNF, $R = 0.46$, $p < 0.01$), suggesting a common mechanism for the enhancement of memory. However, unlike protein levels of BDNF, the regional enhancement of BDNF mRNA expression in the hippocampus appeared to be predominantly enhanced by anthocyanins. The present data support the claim that flavonoids are likely causal agents in mediating the cognitive effects of flavonoid-rich foods^[20].

Polyphenols have been reported to exert their neuroprotective actions through the potential to protect neurons against injury induced by neurotoxins, an ability to suppress neuroinflammation, and the potential to promote memory, learning, and cognitive function. Recent evidence suggested that their beneficial effects involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling and neurohormetic effects leading to the expression of genes that encode antioxidant enzymes, phase-2 enzymes, neurotrophic factors, and cytoprotective proteins. Specific examples of such pathways include the sirtuin-Foxo pathway, the NF- κ B pathway, and the Nrf-2/ARE pathway. Together, these processes act to maintain brain homeostasis and play important roles in neuronal stress adaptation and thus polyphenols have the potential to prevent the progression of neurodegenerative pathologies^[21].

Food intake is subject to a complex regulation by the hypothalamus and other brain centers including the brain stem and the hippocampus. An intricate network of interacting feedback mechanisms that involve the neural centers along with the stomach gut, liver, thyroid, and adipose tissue in the periphery, influence the eventual outcome of food intake and satiety. Key peripheral signals, such as leptin, insulin, and ghrelin, have been linked to hypothalamic neuropeptide systems in energy regulation. The author examined the neural centers important in food intake, the role of various neuropeptides, and the neurohormonal influence on food intake. The potential role of polyphenols in influencing the neuroregulatory factors, the neural signaling pathways and/or the peripheral feedback mechanisms that modulate food intake was examined^[22].

Compounds counteracting amyloid aggregation have been investigated for their ability (i) to stabilize toxic amyloid precursors; (ii) to prevent the growth of toxic oligomers or speed that of fibrils; (iii) to inhibit fibril growth and deposition; (iv) to disassemble preformed fibrils; and (v) to favor amyloid clearance. Natural phenols, a wide panel of plant molecules, are one of the most actively investigated categories of potential amyloid inhibitors. They are considered responsible for the beneficial effects of several traditional diets being present in green tea, extra virgin olive oil, red wine, spices, berries and aromatic herbs. Accordingly, it has been proposed that some natural phenols could be exploited to prevent and to treat amyloid diseases, and recent studies have provided significant information on their ability to inhibit peptide/protein aggregation in various ways and to stimulate cell defenses, leading to identify shared or specific mechanisms. The authors showed the significance and mechanisms of amyloid aggregation and aggregate toxicity and summarized the recent achievements on protection against amyloid diseases by many natural phenols^[23].

ALOE VERA GEL TO INSULIN SENSITIVITY

In vitro studies

A high-performance liquid chromatographic analysis (HPLC) has been developed for determination of phenolic ingredients of Aloe species and the distribution of phenolics in gel, inner epidermal layer, terminal bud and root of aloe vera were examined^[24].

Chemical composition of the exudate and gel of aloe vera and contribution of diverse components to therapeutic action of aloe vera

were summarized as a functional ingredient in foods^[25].

Antioxidant components in aloe vera were examined for lipid peroxidation using rat liver microsomal and mitochondrial enzymes. Among the aloesin derivatives examined, isorabaichromone showed a potent antioxidative activity. The 1,1-diphenyl-2-picrylhydrazily (DPPH) radical and superoxide anion scavenging activities were determined. As one of the most potent components, isorabaichromone together with feruloylaloenin and *p*-coumaroylaloenin showed potent DPPH radical and superoxide anion scavenging activities. Electron spin resonance (ESR) using the spin trapping method suggested that the potent superoxide anion scavenging activity of isorabaichromone may have been due to its caffeoyl group. As aloe vera gel has long been used to promote wound healing, the inhibitory effects of aloesin derivatives for cyclooxygenase (Cox) -2 and thromboxane (Tx) A₂ synthase were examined and the participation of *p*-coumaroyl and feruloyl ester groups in the aloesin skeleton was demonstrated. These findings may explain, at least in part, the wound healing effects of aloe vera^[26].

Animal studies

The kidachi aloe (*Aloe arborescens* M.) components inhibited the destruction of rat pancreatic islet β -cells by streptozotocin (Sz) or alloxan (Ax) or hypoxanthine-xanthine (Ho-Xo) oxidase dependent O₂ radicals. These components were prepared in the form of a freeze-dried powder of the boiled leaf skin of kidachi aloe, and measurement of DPPH radical-scavenging activity showed higher radical-scavenging activity in this boiled leaf skin powder than the non-boiled leaf skin powder. Furthermore, HPLC of the boiled leaf skin powder were similar to those of commercially available aloin. Therefore the main component may be a phenolic compound. In addition, the phenolic fraction of the boiled leaf skin contained large amount of 2'-O-*p*-coumaroylaloenin and 2'-O-feruloylaloenin, which have higher DPPH radical-scavenging activity than barbaloin. These results suggest that the action mechanism of kidachi aloe leaf skin components, which prevent destruction of the pancreatic islets by specific pancreatic toxins such as Sz, Ax and Ho-Xo, involves inhibition of free radical-screening effects, and may be associated with a thermostable low molecular component. The co-existence of kidachi aloe-derived 2'-O-*p*-coumaroylaloenin, 2'-O-feruloylaloenin, and barbaloin may result in the potential activation of radical-scavenging activity^[27].

Antidiabetic effects of kidachi aloe were determined. Firstly, ICR mice which received frequent injections of Sz in small doses were fed ad libitum with basal diets supplemented with components of kidachi aloe as following: (1) 2 % kidachi aloe whole leaf diet; (2) 2 % kidachi aloe leaf pulp diet; (3) 2 % kidachi aloe 10 KD fraction diet; (4) aloe vera leaf pulp diet; (5) basal diet. The group 1 and 3 significantly suppressed the elevation of blood sugar as compared to group 5. Secondly, a strong inhibitory action on intestinal glucose absorption was observed in group 3. Thirdly, phenolic compounds, such as aloenin, barbaloin and aloe emodin, derived from kidachi aloe in the blood serum and organs were quantitatively measured by a HPLC following forced administration of aloe components to rats to determine absorption kinetics of aloe components inside the body. The primary component of aloe phenol compounds is the same component obtained from group 3 and it was found in the pancreas and liver in addition to in the blood serum. The above results indicate that fore and aft when Sz injections could cause selective toxicity to β -cells of islets, the dietary administration of 10 KD fraction powder to mice would lead to the persistence of aloe phenol compound having an antioxidant activity in the pancreas and blood, which could

protect islets of Langerhans from the destruction caused by methyl radical derived from Sz. The results suggested the possibility of the 10 KD fraction powder to alleviate the burden of insulin secretion as it has an inhibitory action on glucose absorption in the jejunum of rats^[28].

Ethanol extract of aloe vera exhibited anti hyperglycemic and antioxidant effects in Sz-induced diabetic rats. Aloe vera leaf extract (AV) administered orally to different groups of rat at a dose of 300 mg/kg body weight. The diabetic rats exhibited lower activity levels of superoxide dismutase (SOD), catalase (CAT), glutathion peroxidase (GPx) and glutathion reductase (GR) in hepatic and renal tissues as compared with normal rats. The activities of SOD, CAT, GPx and GR were increased in hepatic and renal tissue of AV treated diabetic rats. The increased level of lipid peroxidation in diabetic rats was also found to be decreased and regenerative liver and kidney histological changes were observed in the AV treated rats^[29].

Aloe QDM which was composed of processed aloe vera gel (PAG) and 2 % aloesin, lowered fasting blood glucose and plasma insulin compared with high fat diet; control, a high-fat diet. Obesity-induced inflammatory cytokine (IL-1 β , -6, -12, TNF- α) and chemokine (CX3CL1, CCL5) mRNA and protein were decreased markedly, as was macrophage infiltration and hepatic triglycerides by aloe QDM. At the same time, aloe QDM decreased the mRNA and protein of PPAR α /LXR α and 11 β -HSD1 both in the liver and white adipose tissue (WAT). Dietary aloe formula reduced obesity-induced glucose tolerance not only by suppressing inflammatory responses but also by inducing anti-inflammatory cytokines in the WAT and liver, both of which are important peripheral tissues affecting insulin resistance. The basic processing methodology used to prepare crude PAG involves incubation of aloe vera gel with cellulase, termination of the reaction by heating, and then passage through a charcoal column to remove anthraquinones and other colored substances^[30].

A polyphenol-rich aloe vera extract (350 mg/kg) with known concentrations of aloin (181.7 mg/kg) and aloe-emodin (3.6 mg/kg) was administered orally for a period of 4 weeks to insulin resistant ICR mice. Pioglitazone (50 mg/kg) and bi-distilled water were used as positive and negative controls, respectively. Body weight, food uptake, and plasma concentrations of insulin and glucose were measured and insulin tolerance tests were performed. The insulin resistance value was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) formula. Results showed that the polyphenol-rich extract from aloe vera was able to decrease significantly both body weight ($p < 0.008$) and blood glucose levels ($p < 0.005$) and to protect animals against unfavorable results on HOMA-IR, which was observed in the negative control group. The highest glucose levels during the insulin tolerance curve test were in the negative control group when compared to the aloe vera extract and pioglitazone treated mice ($p < 0.05$). In conclusion, aloe vera gel could be effective for the control of insulin resistance^[31].

Two aloe chromones, aloesin and aloesinol, were tested in vitro for adiponectin production. Following confirmation of glucose-lowering activity in a high-fat diet (HFD)-induced mouse model, aloesin was formulated with an aloe vera inner leaf gel powder polysaccharide preparation to yield a composition designated UP780. Efficacy of UP780 was evaluated in HFD-induced and db/db mouse models. GW1929, a synthetic peroxisome proliferator-activated receptor- α (PPAR- α) agonist, was used as a positive control. After 3 weeks of treatment of HFD-induced mice, plasma insulin levels were decreased 37.9 % and 46.7 % by aloesin and aloesinol, respectively. In db/db mice, the chromone- (2 % chromone: 98% aloe polysaccharide) enriched UP780 aloe composition showed a 33.7 %

and 46.0 % decrease in fasting triglyceride and plasma glucose levels after 10 weeks of oral treatment, respectively. Diabetic mice gavaged with 200 mg/kg of UP780 for 10 weeks showed a 30.3 % decrease in fasting blood glucose levels and a 32.2 % reduction in plasma insulin. In both animal models, UP780 showed a statistically significant improvement in blood glucose clearance. These findings indicated that UP780, a chromone-standardized, aloe-based composition, could potentially be used as a natural product option to facilitate the maintenance of healthy blood glucose levels^[32].

The effects of processed aloe vera gel (PAG) on the course of established diet-induced non-insulin-dependent diabetes mellitus (NIDDM) were studied in C57BL/6J mice. NIDDM was induced in C57BL/6L mice by feeding them a high-fat diet. Mice exhibiting diet-induced obesity (DIO) with blood glucose levels above 180 mg/dL were selected to examine the antidiabetic effects of PAG. Oral administration of PAG for 8 weeks reduced circulating blood glucose concentrations to a normal level in these DIO mice. In addition, the administration of PAG significantly decreased plasma insulin. The antidiabetic effects of PAG were also confirmed by intraperitoneal glucose tolerance testing. PAG appeared to lower blood glucose levels by decreasing insulin resistance. The administration of PAG also lowered triglyceride levels in liver and plasma. Histological examinations of periepididymal fat pad showed that PAG reduced the average size of adipocytes. These results demonstrated that the oral administration of PAG prevents the progression of NIDDM-related symptoms in high-fat diet-fed mice, and suggested that PAG could be useful for treating NIDDM^[33].

Human study

Defective brain insulin signaling has been suggested to contribute to the cognitive deficits in patients with Alzheimer's disease (AD). Although a connection between AD and diabetes has been suggested, a major unknown is the mechanism(s) by which insulin resistance in the brain arises in individuals with AD.

The authors showed that serine phosphorylation of IRS-1 (IRS-1pSer) is common to both diseases. Brain tissue from humans with AD had elevated levels of IRS-1pSer and activated JNK (c-Jun N-terminal kinase), analogous to what occurs in peripheral tissue in patients with diabetes. The authors found that amyloid- β peptide (A β) oligomer, synaptotoxins that accumulate in the brains of AD patients, activated the JNK/TNF- α pathway, induced IRS-1 phosphorylation at multiple serine residues, and inhibited physiological IRS-1pTyr in mature cultured hippocampal neurons. Impaired IRS-1 signaling was also present in the hippocampi of Tg mice with a brain condition that models AD. Importantly, intracerebroventricular injection of A β oligomer triggered hippocampal IRS-1pSer and JNK activation in cynomolgus monkeys. The oligomer-induced neuronal pathologies observed *in vitro*, including impaired axonal transport, were prevented by exposure to exendin-4 (exenatide), an anti-diabetes agent. In Tg mice, exendin-4 decreased levels of hippocampal IRS-1pSer and activated JNK and improved behavioral measures of cognition. By establishing molecular links between the dysregulated insulin signaling in AD and diabetes, the present results opened avenues for the investigation of new therapeutics in AD^[34].

The role of the gut microbiota in the pathophysiology of obesity and type 2 diabetes, which is promoted by a bacterial diversity shift mediated by overnutrition was reviewed. Whole bacteria, their products, and metabolites undergo increased translocation through the gut epithelium to the circulation due to degraded tight junctions and the consequent increase in intestinal permeability that culminates in inflammation and insulin resistance. Several strategies

focusing on modulation of the gut microbiota (antibiotics, probiotics, and prebiotics) are being experimentally employed in metabolic derangement in order to reduce intestinal permeability, increase the production of short chain fatty acids and anorectic gut hormones, and promote insulin sensitivity to counteract the inflammatory status and insulin resistance found in obese individuals^[35].

The gut microbiota has been identified as a potential contributor to metabolic diseases. It has been shown that obese individuals present different proportions of bacterial phyla compared with lean individuals, with an increase in Firmicutes and Actinobacteria and a decrease in Bacteroidetes. This alteration seems to interfere with intestinal permeability, increasing the absorption of lipopolysaccharide (LPS), which reaches circulation and initiates activation of Toll-like receptor (TLR) 4 and 2 and LPS receptor CD14, leading to increased activation of inflammatory pathways. With these activations, an impairment of the insulin signaling is observed, with decreased phosphorylation of the insulin receptor, insulin receptor substrate (IRS) and Akt, as well as increased inhibitory serine phosphorylation of IRS-1. Altered proportions of bacterial phyla have also been demonstrated to interfere with host's biochemical pathways, increasing energy extraction and depot in adipose tissue. Therefore, understanding the mechanisms by which the alteration in the gut microbiota produces different signaling activations and phenotype changes may offer an interesting opportunity for the treatment of obesity and type 2 diabetes^[36].

The authors studied the effects of infusing intestinal microbiota from lean donors to male recipients with metabolic syndrome on the recipients' microbiota composition and glucose metabolism. Subjects were assigned randomly to groups that were given small intestinal infusions of allogenic or autologous microbiota. Six weeks after infusion of microbiota from lean donors, insulin sensitivity of recipients increased (median rate of glucose disappearance changed from 26.2 to 45.3 $\mu\text{mol/kg/min}$; $p < 0.05$) along with levels of butyrate-producing intestinal microbiota. Intestinal microbiota might be developed as therapeutic agents to increase insulin sensitivity in humans^[37].

A double-blind, placebo-controlled Institutional Review Board (IRB)-approved pilot study of two aloe products (UP780: processed aloe vera gel+2% aloesin and AC952: aloe vera inner polysaccharide gel) in patients with prediabetes over an 8-week period, was studied. A total of 45 subjects with impaired fasting glucose or impaired glucose tolerance and having two other features of metabolic syndrome were recruited ($n=15/\text{group}$). Parameters of glycemia [(fasting glucose, insulin, homeostasis model assessment: HOMA), glycosylated hemoglobin (HbA1c), fructosamine, and oral glucose tolerance test (OGTT)] and oxidative stress (urinary F2-isoprostanes) were measured along with lipid profile and high-sensitivity C-reactive protein (hsCRP) levels before and after supplementation. Compared to placebo, only the AC952 aloe vera inner leaf gel powder resulted in significant reduction in total and low-density lipoprotein cholesterol (LDL-C) levels, glucose, and fructosamine. In the UP780 aloe vera inner gel powder standardized with 2% aloesin group, there were significant reductions in HbA1c, fructosamine, fasting glucose, insulin and HOMA. Only the UP780 aloe group had a significant reduction in the F2-isoprostanes compared to placebo. Standardized aloe preparations offered an attractive adjunctive strategy to revert the impaired fasting glucose and impaired glucose tolerance observed in conditions of prediabetes/metabolic syndrome^[38].

Brain glucose metabolism is impaired in Alzheimer's disease (AD), the most common form of dementia. Type 2 diabetes mellitus (T2DM) is reported to increase the risk for dementia, including

AD, but the underlying mechanism is not understood. The authors investigated the brain insulin-PI3K-AKT signalling pathway in the autopsied frontal cortices from nine AD, ten T2DM, eight T2DM-AD and seven control cases. The authors found decreases in the level and activities of several components of the insulin-PI3K-AKT signalling pathway in AD and T2DM cases. The deficiency of insulin-PI3K-AKT signalling was more severe in individuals with both T2DM and AD (T2DM-AD). This decrease in insulin-PI3K-AKT signalling could lead to activation of glucocorticoid synthase kinase-3 β , the major tau kinase. The levels and the activation of the insulin-PI3K-AKT signalling components correlated negatively with the level of tau phosphorylation and positively with protein O-GlcNAcylation, suggesting that impaired insulin-PI3K-AKT signalling might contribute to neurodegeneration in AD through down-regulation of O-GlcNAcylation and the consequent promotion of abnormal tau hyperphosphorylation and neurodegeneration. The decrease in brain insulin-PI3K-AKT signalling, also correlated with the activation of calpain I in the brain, suggesting that the decrease might be caused by calpain over-activation. The findings provide novel insight into the molecular mechanism by which type 2 diabetes mellitus increases the risk for developing cognitive impairment and dementia in AD^[39].

The age- and sex-adjusted incidence of all-cause dementia, AD and vascular dementia (VaD) were significantly higher in subjects with diabetes than in those with normal glucose tolerance. These associations remained robust even after adjustment for confounding factors for all-cause dementia and AD, but not for VaD (all-cause dementia: adjusted hazard ratio [HR]=1.74, 95 % confidence interval [CI]=1.19 to 2.53, $p=0.004$; AD: adjusted HR=2.05, 95 % CI=1.18 to 3.57, $p=0.01$; VaD: adjusted HR=1.82, 95% CI=0.89 to 3.71, $p=0.09$). Moreover, the risks of developing all-cause dementia, AD, and VaD significantly increased with elevated 2-hour postload glucose (PG) levels even after adjustment for covariates, but no such associations were observed for fasting plasma glucose (FPG) levels: compared with those with 2-hour PG levels of <6.7 mmol/L, the multivariable-adjusted HRs of all-cause dementia and AD significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L or over, and the risk of VaD was significantly higher in subjects with levels of ≥ 11.1 mmol/L. The findings suggested that diabetes is a significant risk factor for all-cause dementia, AD, and probably VaD. Moreover, 2-hour PG levels but not FPG levels, are closely associated with increased risk of all-cause dementia, AD and VaD^[40].

The effect of basal insulin on global and regional brain glucose uptake and metabolism in humans was studied using ¹⁸F-fluoro deoxyglucose and positron emission tomography. Eight healthy male volunteers aged 49.3 \pm 5.1 years were studied twice in random order. On each occasion, they received an infusion of 0.1 mg/kg/min somatostatin to suppress endogenous insulin production. In one study 0.3 mU/kg/min insulin was infused to replace basal circulating insulin level, and in the other study a saline infusion was used as control. The authors sought stimulatory effects of basal insulin on brain glucose metabolism particularly in regions with deficiencies in the blood-brain barrier and high density of insulin receptors. Insulin levels were 27.07 \pm 1.3 mU/L with insulin replacement and 3.51 \pm 0.4 mU/L without ($p=0.001$). Mean global rate of brain glucose utilization was 0.215 \pm 0.030 mmol/kg/min without insulin and 0.245 \pm 0.021 mmol/kg/min with insulin ($p=0.008$, an average difference of 15.3 \pm 12.5%). Regional analysis using statistical parametric mapping showed that the effect of basal insulin was significantly less in the cerebellum ($Z=5.53$, corrected $p=0.031$). The authors concluded that basal insulin has a role in regulating global brain glucose uptake in humans, mostly marked in cortical areas^[41].

A low insulin response at baseline was associated with a higher cumulative risk of AD (hazard ratio for 1 significant difference: SD decrease, 1.31; 95% confidential interval: CI, 1.10-1.56) also after adjustment for age, systolic blood pressure, body mass index, serum cholesterol, smoking, education level, and insulin resistance. This association was stronger in subjects without the apolipoprotein E $\epsilon 4$ allele. Impaired glucose tolerance increased the risk of vascular dementia (hazard ratio for 1 significant difference: SD decrease, 1.45; 95% confidential interval: CI, 1.05-2.00) but not AD. Impaired insulin secretion, glucose tolerance, and estimates of insulin resistance were all associated with higher risk of any dementia and cognitive impairment. In this longitudinal study, impaired acute insulin response at mid-life was associated with an increased risk of AD up to 35 years later suggesting a causal link between insulin metabolism and the pathogenesis of AD^[42].

To analyze the direct effect of insulin on food-related neuronal activity the authors tested 10 lean and 10 obese subjects. The authors conducted a magnet encephalography study during a visual working memory task in both the basal state and after applying insulin or placebo spray intra-nasally to bypass the blood brain barrier. Food and non-food pictures were presented and subjects had to determine whether or not two consecutive pictures belonged to the same category. Intra-nasal insulin displayed no effect on blood glucose, insulin or C-peptide concentrations in the periphery; however, it led to an increase in the components of evoked field related to identification and categorization of pictures (at around 170 ms post stimuli in the visual ventral stream) in lean subjects when food pictures were presented. In contrast, insulin did not modulate food-related brain activity in obese subjects. The authors demonstrated that intra-nasal insulin increases the cerebral processing of food pictures in lean whereas this was absent in obese subjects. This study further substantiates the presence of a cerebral insulin resistance in obese subjects and might be relevant in the pathogenesis of obesity^[43].

Although the epidemiological evidence that insulin resistance associates with cognitive impairment continues to accumulate most of the data remains correlative with little convincing detailed mechanistic proof that neuronal insulin resistance enhances the development of dementia. Indeed mouse knockout studies seem to suggest that the connection is not a simple loss of post-receptor signalling. In the review the authors discussed the difficulties in quantifying insulin sensitivity of the brain and why it is vital that they develop technology for this purpose so that they can establish its role in this new-age dementia^[44].

While a potential causal factor in AD, brain insulin resistance has not been demonstrated directly in that disorder. The authors provided such a demonstration here by showing that the hippocampal formation (HF) and, to a lesser degree, the cerebellar cortex in AD cases without diabetes exhibited markedly reduced responses to insulin signalling in the IR \rightarrow IRS-1 \rightarrow PI3K signalling pathway with greatly reduced responses to IGF-1 in the IGF-1R \rightarrow IRS-2 \rightarrow PI3K signalling pathway. Reduced insulin responses were maximal at level of IRS-1 and were consistently associated with basal elevations in IRS-1 phosphorylated at serine 616 (IRS-1 pS⁶¹⁶) and IRS-1 pS^{636/639}. In the HF, these candidate biomarkers of brain insulin resistance increased commonly and progressively from normal cases to mild cognitive impaired cases to AD cases regardless of diabetes or APOE $\epsilon 4$ (apolipoprotein E, gene $\epsilon 4$) status. Levels of IRS-1 pS⁶¹⁶ and IRS-1 pS^{636/639} and their activated kinases correlated positively with those of oligomeric A β (amyloid β) plaques and were negatively associated with episodic and working memory, even after adjusting for A β plaques, neurofibrillary tangles, and APOE $\epsilon 4$. Brain insulin

resistance thus appears to be an early and common feature of AD, a phenomenon accompanied by IGF-1 resistance and closely associated with IRS-1 dysfunction potentially triggered by A β oligomers and yet promoting cognitive decline independent of classic AD pathology^[45].

A pilot clinical trial was performed to examine the effects of intranasal insulin administration on cognitive function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnesic mild cognitive impairment or AD. Participants received placebo ($n=30$), 20 IU of insulin ($n=36$), or 40 IU of insulin ($n=38$) for 4 months, administered with a nasal drug delivery device. Outcome measures were analyzed using repeated-measures analysis of covariance. Treatment with 20 IU of insulin improved delayed memory ($P<0.05$), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability ($P<0.01$). Both insulin doses also preserved general cognition as assessed by the ADAS-cog (AD assessment scale-cognitive subscale) score for younger participants and functional abilities as assessed by ADCS-ADL (AD cooperative study-activities of daily living) scale for adults with AD ($P<0.05$). Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the A β 42 level and in the tau protein-to-A β 42 ratio in cerebrospinal fluid. Placebo-assigned participants showed decreased ¹⁸F-deoxyglucose uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression. No treatment-related severe adverse events occurred. These results support longer trials of intranasal insulin therapy for patients with amnesic mild cognitive impairment and patients with AD^[46].

The quality control of protein homeostasis deteriorates with aging, causing the accumulation of misfolded proteins and neurodegeneration. Thus, in AD, soluble oligomers, protofibrils and fibrils of A β and tau protein accumulate in specific brain regions. This is associated with the progressive destruction of synaptic circuits controlling memory and higher mental function. The primary signalling mechanisms that (i) become defective in AD to alter the normal proteostasis of A β and tau, and (ii) initiate a pathophysiological response to cause cognitive decline, are unclear. The IIS (insulin/IGF-1-like signalling) pathway is mechanistically linked to longevity, protein homeostasis, learning and memory, and is emerging to be central to both (i) and (ii). This pathway is aberrantly overactivated in AD brain at the level of increased activation of the serine/threonine kinase AKT (protein kinase B) and phosphorylation of its downstream targets, including mTOR (mammalian target of rapamycin). Feedback inhibition of normal insulin/IGF activation of the pathway also occurs in AD due to inactivation of IRS-1 (insulin receptor substrate 1) and decreased IRS-1/2 levels. Pathogenic forms of A β may induce aberrant sustained activation of the PI3K (phosphoinositide 3-kinase)/AKT signal in AD, also causing non-responsive insulin and IGF-1 receptor, and altered tau phosphorylation, conformation and function. Reducing IIS activity in animal models by decreasing IGF-1 levels or inhibiting mTOR activity alters A β and tau protein homeostasis towards less toxic protein conformations, improves cognitive function and extends healthy lifespan. Thus normalizing IIS dysfunction may be therapeutically relevant in abrogating A β and tau proteotoxicity, synaptic dysfunction and cognitive decline in AD^[47].

Aging is the most significant risk factor for T2DM and especially for AD and both pathologies share insulin resistance and impaired energy metabolism indicating that both can be considered as metabolic diseases thus opening the door to common and/or complementary diagnostic and therapeutic approaches. On these results, it is possible that lifestyle modifications, diet, micro-and

macro-nutrients supplements, and consumption of natural food substances rich in antioxidants, from early age, supported from aerobic exercise could prevent, retard or cure these diseases^[48].

The authors discussed the results of intranasal insulin studies that have demonstrated that enhancing brain insulin signaling improves memory and learning processes in both cognitively healthy and impaired humans. The authors provided an overview of neuroimaging studies indicating that disturbances in insulin metabolism-such as insulin resistance in obesity, type 2 diabetes and AD-and altered brain responses to insulin are linked to decreased cerebral volume and especially to hippocampal atrophy^[49].

The authors work has focused on identifying the relationship of the insulin network to brain aging, and determining the mechanisms through which insulin dysregulation promotes AD pathological processes. Candidate mechanisms include the effects of insulin on A β , cerebral glucose metabolism, vascular function, lipid metabolism, and inflammation/oxidative stress. It is likely that different nodes of the insulin network are perturbed for subgroups of AD patients, or that for some subgroups, pathways independent of insulin are critical pathogenetic factors. New methods from systems network analyses may help to identify these subgroups, which will be critical for devising tailored prevention and treatment strategies. In this review, the authors provide a brief description of the role of insulin in normal brain function, and then focus more closely on recent evidence regarding the mechanisms through which disruption of that role may promote AD pathological processes. The authors discuss the implications of this area for AD therapeutics and prevention^[50].

A previous clinical trial demonstrated that four months of treatment with intranasal insulin improves cognition and function for patients with AD or mild cognitive impairment (MCI), but prior studies suggest that response to insulin treatment may differ by sex and ApoE ϵ 4 carriage. Thus, responder analyses using repeated measures analysis of covariance were completed on the trial's 104 participants with MCI or AD who received either placebo or 20 or 40 IU of insulin for 4 months, administered by a nasal delivery device. Results indicated that men and women with memory impairment responded differently to intranasal insulin treatment. On delayed story memory, men and women showed cognitive improvement for the 40 IU dose. The sex difference was most apparent for ApoE ϵ 4 negative individuals. For the 40 IU dose, ApoE ϵ 4 negative men improved while ApoE ϵ 4 negative women worsened. Their ApoE ϵ 4 positive counterparts remained cognitively stable. This sex effect was not detected in functional measures. However, functional abilities were relatively preserved for women on either dose of intranasal insulin compared with men. Unlike previous studies with young adults, neither men nor women taking intranasal insulin exhibited a significant change in weight over 4 months of treatment^[51].

The insulin/insulin-like growth factor 1 (IGF-1) signaling pathway is evolutionary conserved in diverse species including *Caenorhabditis elegans*, *Saccharomyces cerevisiae*, *Drosophila melanogaster*, rodents and humans, which is involved in many interrelated functions that are necessary for metabolism, growth and reproduction. Interestingly, more and more research has revealed that insulin/IGF-1 signaling pathway plays a pivotal role in the regulation of longevity. Generally, distribution of the power of this pathway will extend longevity in species ranging from *C.elegance* to humans. The role of insulin/IGF-1 in longevity is probably related to stress resistance. Although the underlying mechanisms of longevity are not fully understood, the insulin/IGF-1 signaling pathway has attracted substantial attention and it will be a novel target to prevent or postpone age-related diseases and extend life span. In present

review, the authors mainly focus on the similar constitution and role of insulin/IGF-1 signaling pathway in *C.legans*, *S. cerevisiae*, rodents and humans^[52].

Longevity extension in *D.melanogaster* by feeding diet supplemented with chemicals throughout adulthood can cause harmful side effects. The authors tested the effect of larva diet supplementation with five different concentrations of resveratrol and one concentration of aloe vera extract on the adult longevity of short-lived *D.melanogaster* population. Resveratrol and aloe vera extract supplementation of larval diet extended adult longevity in both the male and female flies without reducing fecundity but by efficient reactive oxygen species scavenging through increased antioxidant enzymes activity and better neuroprotection as indicated by increased locomotor activity in adult males^[53].

Influence of long-term aloe vera ingestion was investigated on age-related disease in male Fisher 344 rats. Life-long aloe vera ingestion does not cause any obvious harmful and deleterious side effects, and could also be beneficial for the prevention of age-related pathology^[54].

Alzheimer's disease (AD) is a leading killer of Americans, imparts a significant toll on the quality of life the patients and primary caregiver, and the results in inordinate costs in an already overburdened medical system. Prior studies on cholinesterase inhibitors among AD patients have shown minimal amelioration of disease symptoms and/or restoration of lost cognitive functioning. The effect of improved nutrition, particularly with dietary supplementations, on cognitive functioning may offer an alternative strategy compared to standard treatment. The present pilot study investigated the effect of an aloe polymannose multnutrient complex (APMC) formula on cognitive and immune functioning over 12 months among adults diagnosed with AD. Subjects participated in an open-label trial and consumed 4 teaspoons per day of the APMC. The AD assessment scale-cognitive subscale (ADAS-cog), mini mental state examination (MMSE), modified AD corporative study activity of daily living inventory (ADCS-ADL), and severe impairment battery (SIB), were administered at baseline and 3, 6, 9, and 12 months follow-up. Cytokines and lymphocyte and monocyte subsets were assessed at baseline and 12 months. The mean ADAS-cog cognition score significantly improved at 9 and 12 months. The mean ADAS-cog cognition score significantly improved at 9 and 12 months from baseline, and 46% of the sample showed clinically-significant improvement (≥ 4 -point change) from baseline to 12 months. Participants showed significant decreases in tumor necrosis factor- α , vascular endothelial growth factor, and interleukins-2 and -4. CD90+, CD95+CD3+, CD95+CD34+, CD95+CD90+, CD14+CD34+, CD14+CD90+, and CD14+CD95+ decreased significantly, whereas CD14+ significantly increased. Participants tolerated the APMC supplement with few, temporary adverse reactions. The authors showed improvements in both clinical and physiological outcomes for a disease that otherwise has no standard ameliorative remedy^[55].

CONCLUSION

Metabolism and immunity are inextricably linked to both to each other and to organism-wide function, allowing mammals to adapt to diverse changes in their intestinal and external environments.

Dietary plant polyphenols and polyphenol-rich nutrients modulate carbohydrate and lipid metabolism, attenuate hyperglycemia, dyslipidemia and insulin resistance, improve adipose tissue metabolism, and alleviate oxidative stress and stress-sensitive signaling pathways and inflammatory process. Polyphenolic

compounds can also prevent the development of long-term diabetes complications including cardiovascular disease, neuropathy, nephropathy and retinopathy^[56].

Among phenolic ingredients in aloe vera gel, barbaloin, aloesin and salicylate with aloe polymannose and its oligomers (MOS) have particularly been investigated for the stimulation of insulin sensitivity in diabetes subjects.

Recent randomised preclinical trials in short-duration studies of salsalate (a dimer of salicylate, one of the ingredient in aloe vera) were evaluated in 286 participants at 3 private practices and 18 academic centers in USA. Salsalate improved glycemia in patients with type 2 diabetes and decreased counts of inflammatory mediators, such as circulating leukocyte, neutrophil, and lymphocyte. Continued evaluation of mixed cardio-renal signals was warranted; urinary albumin levels increased but reversed on discontinuation; estimated glomerular filtration rates were unchanged^[57].

Further investigations using clinical studies are needed, (1): to confirm the beneficial effects of polyphenolic ingredients with aloe polymannose and MOS to gut-brain (hypothalamus) axis of hepatic glucose production and insulin sensitivity; (2): to determine the role of insulin-potentiating and antioxidant phenolics on improved brain insulin signaling and cognitive function; (3): to examine the mechanisms by which anti-oxidatant phenolics in aloe vera gel metabolites protect neuron cells from varying levels of glucose and A β toxicity. Furthermore, molecular analysis of gut microbial changes in long-term aloe vera ingestion is needed to prevent age-related diseases in elderly.

An assumption based on a brain-liver-intestine circuit to coordinate with insulin sensitivity of endogenous glucose production was proposed in present review by figure 1.

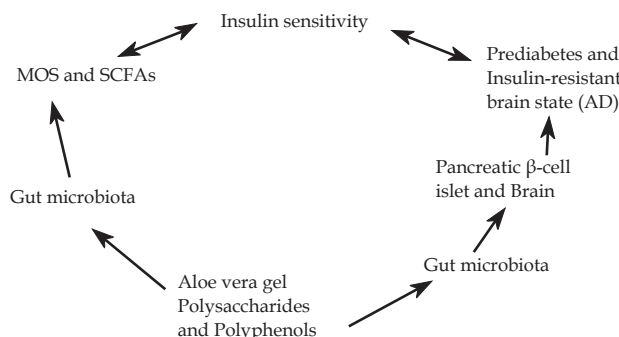


Figure 1 Possible efficacy of aloe vera gel metabolites in long-term ingestion to insulin sensitivity.

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