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Exploratory Approaches for the Use of Aloe for Covid-19 Treatment: Prevention and Mitigation Effect

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ABSTRACT

The global coronavirus disease (COVID)-19 pandemic has become a huge threat to humans. Intensive research on the pandemic mechanisms used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is urgently needed-notably to identify potential drug targets. Clinical studies of patients with COVID-19 have shown that gastrointestinal disorders appear to precede or follow the respiratory symptoms. Here we review exploratory approaches for the use of aloe for COVID treatment, gastrointestinal disorders in patients with COVID-19, suggest hypothetical mechanisms leading to gut symptoms, and discuss the potential consequences of gastrointestinal disorders on the outcome of the disease. Lastly, we discuss the role of the gut microbiota during respiratory viral infections and suggest that targeting food supplement and gut dysbiosis by use of *Aloe vera* may help to control immunomodulatory effect to the pathogenesis of COVID-19.

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Introduction

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 and well studies against the viral receptors by using the molecular docking technique were reported [1]. Candel et al have applied a drug approach of computational methodology, depending on the synergy of molecular docking and viral screening techniques, aimed to identify possible potent inhibitors against COVID-19 from FDA approved antiviral compounds and from the library of active phytochemicals [2]. 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 Medical 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 (an anthraquinone from *Aloe* species) -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.

Pandit and Latha aimed at employing computational approach to screen phytochemicals from the medicinal plants targeting the proteins of SARS-COV-2 for identification of antiviral therapeutics [3]. The study focuses on three target proteins important in the life cycle of SARS-COV-2 namely Spike glycoprotein, main protease and RNA-dependent RNA-polymerase. Molecular docking was performed to screen phytochemicals in medicinal plants to determine their feasibility as potential inhibitors of these target viral proteins. Of the 30 plant phytochemicals screened, phytochemicals from *Tinospora cordiofolia* and *Aloe barbadensis* (*Aloe vera*) displayed good binding energetic with the target proteins in SARS-COV-2.

These results provide a basis for the use of traditional medicinal plants as alternative lines of treatment for COVID-19 infection.

Function of Angiotensin-Converting Enzyme (ACE)-2 and Bradykinin Receptor B1/2 in COVID-19: A Comprehensive Pathophysiological Approach

In our previous studies we identified bradykinin degrading carboxyl peptidase N- and P-like glycoprotein in *Aloe saponaria* and *A. arborescens* and Bautista-Prez et al fractionated anti-bradykinin activity of *A. barbadensis* gel. Bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is a nonapeptide that causes blood vessels to dilate, and therefore causes blood pressure to lower, vasodilation of arteries, vein of gut and stimulates pain receptors [4, 5 & 6]. In human, bradykinin is broken down by three proteolytic

kinases: angiotensin-converting enzyme, amino peptidase, and carboxypeptidase N, which cleave the 7-8, 1-2, and 8-9 positions, respectively.

COVID-19 binds to human angiotensin-converting enzyme 2 (ACE2) to enter the host cells. Tolouian et al discussed the potential therapy for treatment of COVID-19 infection-induced acute respiratory distress syndrome [7]. One of the activities of ACE2 is hydrolyzing the active bradykinin metabolite [des-Arg973] BK (DABK). A decreased activity or reducing expression of ACE2 by the virus impairs the inactivation of DABK. This enhances its signaling through the bradykinin B1 receptor and could lead to fluid extravasation and leukocyte recruitment to the lung. Targeting the bradykinin system by either blocking the bradykinin production or blocking bradykinin receptors may open a new potential therapeutic window for treatment of COVID-19 induced acute respiratory distress syndrome particularly before patients enter the irreversible stages.

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 through 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 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 [8]. 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 administrations. 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. The authors proposed that blocking the B1 and B2 receptors might have an ameliorating effect on disease caused by COVID-19. This kinin-dependent pulmonary edema is resistant to corticosteroids or adrenaline and should be targeted as long as the virus is present. Long lasting vascular leakage and inflammation of the blood vessels will trigger the coagulation cascade leading to thrombosis and eventual scarring of the lungs. When the virus affects the renin-angiotensin-system, the body regulates bradykinin runs amok, bradykinin receptors are re-sensitized, and the body stops breaking down bradykinin, which is typically degraded by ACE. This is believed to be the bradykinin storm that is responsible for many of COVID-19's deadliest symptoms. The authors theorized that a dysregulated bradykinin system was causing leaky blood vessels in the lungs, which was a potential cause of the excess fluid accumulation.

Radical Scavenging Glycoprotein (Verectin) Inhibiting Cyclooxygenase-2 and Thrombosis, and Anti-Inflammatory Active Aloe vera Gel

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 A2 synthase level in vitro [9]. Kishore K suggested that the antithrombotic effect of aloe vera gel aqueous extract is due to its antioxidant property because oxidants play a significant role in hyper-coagulation of blood [10]. The results suggest that aqueous extract of aloe vera gel is a promising antithrombotic plant-based agent. Vazquez et al investigated the capacity of the aqueous extract of aloe vera gel to inhibit Cox activity [11]. The aqueous and chloroform extract decreased the edema induced in the hind-paw and the number of neutrophils migrating into the peritoneal cavity, whereas the ethanol extract only decreased the number of neutrophils. The anti-inflammatory agent indomethacin and dexamethasone also decreased carrageenan-induced edema and neutrophil migration. The aqueous extract inhibited prostaglandin E2 production from ^{14}C arachidonic acid. The results demonstrated that the extract of aloe vera gel have anti-inflammatory activity and suggested its inhibitory action on the arachidonic acid pathway via Cox.

The Suppression of Cytokine Storm: A Potential Role of IL-6, IL-10, IL-1β and TNFα in COVID-19 Pathogenesis

Currently, clinical trials are underway to treat the therapeutic efficacy of blocking agents. Preliminary results from using blocking/neutralizing antibodies against IL-6/IL-6R suggest that further improvement is necessary to lower mortality in COVID-19 patients. By attempting to block its pathological pro-inflammatory function, a unique feature of the cytokine storm in COVID-19 is dramatic elevation of IL-10. This was thought to be negative feedback mechanism to suppress inflammation. Del Valle et al implemented rapid multiplex cytokine assay to measure serum IL-6, IL-8, TNFα and IL-1β in hospitalized patients with COVID-19 upon administration to the hospital and proposed that serum IL-6 and TNFα levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options [12]. Huang et al reported the epidemiological, clinical, laboratory, and radiological characteristic and treatment and clinical outcomes of these patients [13]. Compared with non-COVID-19 patients, ICU patients had higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNFα.

Effect of Aloe vera on Survivability, Extent of Proteolysis and ACE Inhibition of Potential Probiotic Cultures in Fermented Milk: Beneficial Effect of Butyrate Fermented

Effect of Aloe vera gel on angiotensin converting enzyme (ACE) inhibitory activity, extent of proteolysis during fermentation and survival of *Lactobacillus casei* NCDC19 during storage of fermented milk was studied by Basannavar et al [14]. Among the different cultures screened for ACE inhibitory activity, *Lactobacillus casei* NCDC 19 exhibited the highest ACE inhibition as well as extent of proteolysis in the presence of aloe vera gel an increase in extent of proteolysis and percent ACE inhibitory activity was observed in comparison to control. Al-Madboly et al investigated that the prebiotic activity of aloe vera gel juice was assessed by the participation of short chain fatty acids, such as acetic, propionic, lactic and butyric acid, during 24 h-incubation with *L. fermentum* [15].

Archer and Kremer reported the use of microbial accessible and fermentable carbohydrates and/or butyrate as supportive treatment of patients with COVID-19 infection [16]. Short chain fatty acid butyrate benefits patients with established allergic lung inflammation. Specifically, butyrate has been shown to affect eosinophil trafficking and is able to "blunt migration into the lung, to reduce airway eosinophilia, and to ameliorate impaired lung function". The inflammation accompanying SARS-CoV-2 infection is reflected by high blood levels of C-reactive protein, TNF-α and several interleukins are most notably pro-inflammatory IL-6. Elevated IL-6 in severe COVID-19 patients is a predictor of higher mortality rates. Some successes have been reported after treatment of COVID-19 patients with anti-inflammatory agents such as prednisone, and other anti-inflammatory drugs, including the IL-6 antagonist Tocilizumab. Butyrate has definitively been found to lower IL-6 levels in both animal and human studies. IL-6 causes hyper-coagulation. The use of butyrate enemas

has been reported for multiple conditions including ulcerative colitis, diversion colitis, radiation proctitis, and pouchitis. Studies have yielded varying results making interpretation difficult. The proposed use of butyrate by enema would accomplish two things: Direct application of butyrate to the site of the intestinal tract, terminal ileum and right colon that contains one of the highest concentrations of SARS-Cov-2 receptors, and increase butyrate absorption for systemic distribution since the colon is the primary site of both production and absorption of butyrate.

Crosstalk between Gut Microbiota Dysbiosis, ACE 2 and COVID-19

Viana et al reviewed the outlines of the evidence linking abnormal ACE2 functions with the poor outcomes (higher disease severity and mortality rate) in COVID-19 patients with pre-existing age-related comorbidities and addresses a possible role for microbiota dysbiosis [17]. Trottein and Sokol reported the potential roles of the gut microbiota in COVID-19 outcomes [18]. Clinical studies have demonstrated that the presence of a gastrointestinal disorder in COVID-19 patients is associated with a more aggressive clinical course, including acute respiratory disease syndromes, liver injury, a higher body temperature, and shock. Moreover, the risk factors for severity and mortality in COVID-19 (such as diabetes) are known to be associated with disturbances of the intestinal microbiota and in particular, low production of short chain fatty acids. This is particularly the case for patients with metabolic syndrome (obesity, high blood pressure, and diabetes) who exhibit severity factors for viral infections including respiratory infections.

It was confirmed that human ACE2 is the receptor for the entry of COVID-19 into lower respiratory tract epithelial cells. Given this observation, it is thus expected that the virus could be inhibited if we decrease the expression of ACE2. By screening two databases; Connectivity Map (CMap) and jeaMoon Map (JMap), Cui et al identified a number of candidate agents that decrease ACE2 expression [19]. JMap analysis revealed a number of compounds, among which valproic acid and butyric acid--, etc. were contained. Changes in the composition and functional activity of the gut microbiota and impairment of the gut's barrier function contribute to disease outcomes, including acute respiratory disease syndromes, a systematic cytokine storm, and multi-organ dysfunction.

Possible link of Gut Microbiota and COVID-19; Gut Microbiota and the Gut-lung Axis

Gut microbiota diversity is decreased in old age and COVID-19 has been mainly fatal in elderly patients. Improving gut microbiota profile by personalized nutrition and supplementation known to improve immunity can be one of the prophylactic ways by which the impact of this disease can be minimized in old people and immune-compromised patients. Microbial action on dietary fiber is known to increase short chain fatty acids in blood thereby protector against allergic inflammation in the lungs. Dhar and Mohanty reviewed gut microbiota and COVID-19-possible link and implications [20]. Butyrate, a well-known epigenetic HDAC inhibitor, was shown to induce cell cycle arrest, differentiation, microRNA expression, and apoptosis in colorectal cancer. Possible role of the gut microbiota in modulating immune response in COVID-19 was discussed. Gut microbiota can influence immune response thereby affecting the disease progression. It is important to see the effect of co-supplementation of personalized functional food including prebiotics/probiotic along with current therapies.

Prevention and Mitigation Effects of COVID-19

Viral infections such as that associated with COVID-19 could potentially be mitigated using lifestyle strategies that include a diet rich in whole plants, complete with soluble and insoluble fiber to enhance the immune system and reduce inflammation. In this manner, the probability of being infected may be reduced, and the severity of disease mitigated. Maguire summarized: Controlling one' exposome, including diet, may be one important means to limit infection and control the ensuing inflammation and immune system dysfunction elicited by the SARS-CoV-2 virus; Inclusion of a rich variety of fruits, vegetables, fiber and whole grains that enhances immune function and helps to resolve inflammation holds potential as a strategy to better disease prevention and outcomes during the COVID-19 pandemic [21]. The follow-on public health measures, in order to be more effective, should include careful consideration of the exposome and nutritional needs to better prevent and mitigate infectious diseases. (Exposome: a measure of the effects of life-long environmental exposures on health)

Potential Role of Cellular miRNAs in Coronavirus-Host Interplay

Host miRNAs are known as important regulators of virus replication and pathogenesis. Nersisyan et al performed computational prediction of high-confidence direct interactions between miRNAs and seven human coronavirus RNAs [22]. The authors identified six miRNAs (miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p and miR-4219) with high binding probability across all analyzed viruses. Further bioinformatics analysis of binding sites revealed high conservativity of miRNA binding regions within RNAs of human coronaviruses and their strains. In order to discover the entire miRNA-virus interplay the authors analyzed lungs miRNome of SARS-CoV-2 infected mice using publicly available miRNA sequencing data. The authors found that miR-21-3p has the largest probability of binding the human coronavirus RNAs and being dramatically up-regulated in mouse lungs during infection induced by SARS-CoV-2. (The expression of miR21-3p, previous named miR-21*, increased after berberine treatment in the HepG2 human hepatoma cell line.)

MicroRNA as a Biomarker and Therapeutic Candidate for Patients with Diabetes and COVID-19

In diabetes, differential expression of circulating miRNAs could be a potential biomarker for severity of COVID-19 disease with and without cardiac dysfunction. Diabetes also increases thrombosis and reduces cardioprotective miRNAs such as miR-133a in the heart. In the heart, miRNAs involved in regulation of ACE2 expression, arrhythmia, and sudden cardiac arrest are of great interest for patients with COVID-19 due to their potential roles in SARS-CoV-2 protein expression and heart failure. The studies of Mishara et al suggested that increasing the cardiac levels of miR-133a in the diabetic heart reduces cardiac lipid accumulation [23]. Thus miR-133a could regulate lipotoxicity and metabolic remodeling in the diabetic heart. And it targets angiotensinogen and thus could be involved in regulation of ACE2 receptor function in congestive heart failure condition. MiR-133a is one of the most abundant miRNAs in the human heart, which is downregulated in human diabetic and nondiabetic heart failure. Thus miR-133a is a promising candidate for investigating its role in heart failure in patients with diabetes and COVID-19.

Using Probiotics to Flatten the Curve of COVID-19 Pandemic

At a time when doctors are using drugs with little anti-COVID-19 data, probiotic strains documented for antiviral and respiratory activities should become part of the armamentarium to reduce the burden and severity of this pandemic. Use of recognized prebiotics (e.g., fructan, galactan and aloe-mannan) to enhance propagation of probiotic strains and indigenous beneficial microbes should be recommended as part of the overall strategy to flatten the

curve. Baud et al discussed the mechanistic basis for the action of probiotics to prevent infections and relevance to COVID-19 [24]. An RCT with *Lactobacillus plantanum* DR7 showed suppression of plasma pro-inflammatory cytokines (IFN-γ, TNF-α) in middle-aged adults, and enhancement of anti-inflammatory cytokines (IL-4, IL-10) in young adults, along with reduced plasma peroxidation and oxidative stress levels. Therefore probiotic strains documented to enhance the integrity of tight junctions, for example through increasing butyrate, a fuel for colonocytes could theoretically reduce SARS-CoV-2 invasion.

Butyrate as Supportive Treatment for Patients with Coronavirus SARS-COV-2 Infection

In addition to symptoms of fever, cough, and dyspnea, SARS-COV-2 infection has been reported to produce gastrointestinal (GI) symptoms. Up to 50% of coronavirus cases reported from China had GI related symptoms, with recent corroboration in the United States. The short chain fatty acid butyrate benefits patients with established allergic lung inflammation. Specially, butyrate has been shown to affect eosinophil trafficking and is able to "blunt migration into the lung, to reduce airway eosinophilia, and to ameliorate impaired lung function". Under siege by SARS-COV-2, and perhaps due to over-stimulation of the gut associated lymphoid tissue, host defenses launch a counterattack releasing massive amounts of cytokines, resulting in a "Cytokine storm". Archer and Kramer exhibited that the proposed application of butyrate by enema would accomplish two things: Direct application of the site of the intestinal tract, terminal ileum and right colon that contains one of the highest concentration of SARS-COV-2 receptors, and Increase butyrate absorption for systemic distribution since the colon is the primary site for both production and absorption of butyrate [16].

Potential Inhibitors of SARS-CoV-2 Main Protease from Aloe vera Compounds

SARS-CoV-2 is the pathogen agent of the new corona virus disease that appeared at the end of 2019 in China. COVID-19 is an emerging infectious disease caused by a strain of SARS-CoV-2. SARS-CoV spike (S) protein, a type I membrane-bound protein, is essential for the viral attachment to the host cell receptor angiotensin-converting enzyme 2 (ACE2). As one of aloe constituents for the treatment of COVID-19 infection, Candel et al reported that aloe-emodin can be used as potential blocker against COVID-19 main protease ACE2 [2]. Ho et al showed that emodin significantly blocked the S protein and ACE2 interaction in a dose-dependent manner [25]. Emodin and aloe-emodin can stave off the COVID-19 infection via competing with S-protein in binding to ACE2.

Mpiana et al showed in a survey of literature that Aloe vera can be used as potential anti COVID-19 plant regarding its antiviral activity [26]. The results obtained show that Aloe vera possesses not only antiviral properties but also anti-inflammatory and immune-stimulant properties which can be useful in the management of COVID-19. The authors furthermore designed to identify the potential inhibitors from the set of 10 compounds of *Aloe vera* by means of molecular docking and ADMET properties of the inhibitors using SwissADME and preADME server, Korea [27]. The authors reported a molecular docking study of ten aloe vera molecules with the main protease (SARS-Cov 3CLprotease) responsible for the replication of coronaviruses. The outcome of their molecular simulation and ADMET properties reveals three potential inhibitors of the enzyme (ligands feraloide, aloesin and 9-dihydroxyl-2-O-(2)-cinnamoyl-7-methoxy-aloesin) with a clear preference of ligand feraloide that has the highest binding energy and fully obeys the Lipinski's rule of five. (Feraloide is a new dihydroisocoumarin isolated originally from *Aloe ferox*.) The Lipinski's rule of five based-on ADMET analyses confirms the ligand feraloide to be the best drug candidate.

Aloe vera Downregulates LPS-Induced Inflammatory Cytokine, IL-1β, and IL-10 Production

Budai et al determined the effect of aloe vera containing 96% gel (International Aloe Science Council certified products) on the molecular mechanisms of Nlrp3 inflammasome-mediated IL-1β production in LPS-activated human THP-1 cells and monocyte-derived macrophages [28]. The results showed that aloe vera significantly reduced IL-8, TNFα, IL-6 cytokine production in a dose dependent manner. The authors found that aloe vera inhibited the expression of pro-IL-1β, Nlrp3, caspase-1 as well as that of the P2X7 receptor in the LPS-induced primary macrophages. Aloe vera-mediated strong reduction of IL-8 appears to be the consequence of the reduced expression of both pro-IL-1β as well as Nlrp3 inflammasome components via suppressing specific signal transduction pathways. The expression of the ATP sensor P2X7 receptor is also downregulated by aloe vera that could contribute to the attenuated IL-1β cytokine secretion. Aloe vera products containing 96% inner gel downregulates pro-inflammatory cytokine, IL-1β, production in activated human macrophages.

Aloe High Fiber Content reduces their Cytotoxicity and improves their Immunomodulatory Properties

Lopez et al exhibited *in vitro* experiment that Aloe vera inner leaf gel production (ILG), treated with activated carbon in order to reduce the aloin content and spray dried at relatively low temperature, exhibited more advantageous properties (low toxicity and anti-inflammatory effect; an increase of pro-inflammatory cytokine release of TNF-α and IL-10) than the recently introduced aloe inner gel with high fiber content. Aloe inner leaf gel was dried at ~80°C and mashed to a powder rich in high molecular weight fibers and soluble polysaccharide (ILF) [29]. At lower concentrations (250mg/L) with lipopolysaccharide challenged macrophage-like THP-1 cells decreased by 40% the release of the anti-inflammatory cytokine IL-10, whereas the release of the pro-inflammatory cytokine IL-1β increased by 35% (compared to untreated but challenged macrophage-like THP-1 cells). Under the same condition the less cytotoxic ILG and aloe whole leaf powder (WLP), both samples with a lower fiber content, significantly increased (up to 2.4 times) the release of IL-10, while the concentration of IL-1β remained unaltered and of TNFα decreased by 35%. A treatment of the ILF sample with activated carbon reduced its cytotoxicity and increased the IL-10 release (3.1 times). Since the products, ILG and WLP were not treated with active carbon, a cytotoxic principle is not removed and by having high fiber content, may promote pro-inflammatory effects. The opposite effect was exhibited by the sample with the high fiber and olysaccharide content (ILF) at 0.05X: while the pro-inflammatory cytokine IL-1β increased slightly by 35%, the anti-inflammatory cytokine IL-10 decreased by 40%. The authors suggest applying an activated carbon treatment on aloe-starting products, which have high fiber content and have received high temperature treatment, in order to reduce their cytotoxicity and improve their immunomodulatory properties.

Aloe vera Oligosaccharides reduce the Production of IL-10 after Exposure to Ultraviolet Radiation

Byeon et al investigated that oligosaccharides prepared from purified aloe vera polysaccharide prevented suppression of delayed

type hypersensitivity (DTH) responses in vivo and reduced the amount of IL-10 observed in ultraviolet irradiated murine epidermis [30]. To assess the effect of aloe oligosaccharides on keratinocytes, Pam 212 cells were exposed in vitro to ultraviolet radiation and treated for 1 h with aloe oligosaccharides. Culture supernatants were collected at 24 h later and injected into mice. Supernatants from ultraviolet irradiated keratinocytes suppressed the induction of DTH responses, whereas aloe oligosaccharide treatment reduced IL-10 and blocked the suppressive activity of the supernatants. Application of aloe vera poly/oligosaccharides to UV-irradiation skin prevents photo-suppression of delayed-type hypersensitivity (DTH) responses in mice. The authors exhibited that treatment of keratinocytes with immune-protective carbohydrates, such as tamarindo-xyloglucans and aloe vera poly/oligosaccharides, reduced IL-10 production by app. 50% compared with the cells treated with UV-radiation alone and completely blocked suppressive activity of the culture supernatants in vivo [31].

Increased IL-10 level in COVID-19 Cytokine Storm

Mortality of COVID-19 patients is caused by severe pneumonia and vital organ damage with the involvement of many pro-inflammatory mediators. Currently, clinical trials are underway to test the therapeutic efficacy of blocking agents, either alone or in combination with more than ten inflammatory mediators reported as highly elevated in COVID-19 patients presenting a cytokine storm. Lu et al proposed that using a neutralizing antibody to block IL-10 to limit its potential immune-activating effects in the initiation phase of COVID-19 may be worth testing [32]. One of the interesting in cytokine storm is the dramatic elevation of IL-10. This was thought to be a negative feedback mechanism to suppress inflammation. However, several lines of clinical evidence suggest that dramatic early IL-10 elevation may play a pathological role in COVID-19 severity. The authors showed IL-10 might constitute a potential target to reduce COVID-19 mortality. As such, the timing of blocking IL-10 activity in severe/critically ill COVID-19 patients might be crucial.

Exploratory Approach of Aloe Bradykininase and Aloe Constituents for COVID-19 Treatment

ACE2 is known to play a role in maintaining blood pressure throughout the body, which is regulated by the renin-angiotensin-aldosterone system, controlling blood pressure by regulating vasodilation and vasoconstriction. ACE2 keeps bradykinin under control. Bradykinin makes blood vessels leak. When the COVID-19 is introduced, 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. Bradykinin, which makes blood vessels leak, might be missing link in the disease process of COVID-19 [6]. The long lasting vascular leakage and inflammation of the blood vessel will trigger the coagulation cascade leading to thrombosis and eventual scarring of the lungs. Aloe active glycoprotein fractions may play a key role to the coagulation cascade leading to thrombosis and inflammation.

Evident effects of aloe-emodin, emodin, and aloe polysaccharide on the therapy of viral infections and epigenetic factor butyrate that is involved in latency and reactivation in viral infection were reported. Anti-severe acute respiratory syndrome (SARS) coronavirus 3C-like protease effects of aloe-emodin and emodin were discussed in previous paper [33]. Emodin may be considered as a potential lead therapeutic agent in the treatment of SARS.

Role of Gut Microbiota in influencing lung Diseases

Diet, environmental factors and genetics play an important role in shaping gut microbiota which can influence immunity. Gut microbiota diversity is decreased in old age. COVID-19 has been mainly fatal in elderly patients who points to the role and the gut microbiota may play important role in this disease. Improving gut microbiota profile by personalized nutrition and supplementation known to improve immunity can be one of the prophylactic ways by which the impact of this disease can be minimized in old people and immune-compromised patients. Furthermore we reviewed the importance of butyrate, a well-known epigenetic HDAC inhibitor, and the host-microRNA- microbiota interaction in regulation of gut immunity, and discussed recent studies of aloe vera gel to micRNA regulation and micRNA involved in communication between macrophages and natural killer cells [34]. Identification of human micRNAs involved in coronavirus-host interplay becomes crucially important due to the ongoing COVID-19 pandemic.

Zuo et al investigated changes in fecal microbiomes of patients with SARS-CoV-2 infection during hospitalization and associations with severity and fecal shedding of virus [35]. Patients with COVID-19 had significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensal symbionts, at time of hospitalization and at all time-points during hospitalization. Fecal microbiota alterations were associated with fecal levels of SARS-CoV-2 and COVID-19 severity. The baseline abundance of *Coprobacillus*, *Clostridium* correlated with COVID-19 severity; there was an inverse correlation between abundance of *Faecalibacterium prausnitzii* and disease severity. Over the course of hospitalization, *Bacteroides*, which downregulate expression of angiotensin-converting enzyme 2 in murine gut, correlated inversely with SARS-CoV-2 load in fecal samples from patients.

Strategies to alter the gut microbiome may develop gradually to manage gastrointestinal effects of the virus in the COVID-19 patients.

Summary

Decreasing the release of anti-inflammatory cytokine IL-10 and TNFα with aloe inner gel having high molecular weight fiber and soluble polysaccharides was exhibited in vitro. Aloe oligosaccharide treatment reduced IL-10 in vivo. Aloe vera has functionally valuable ingredients exhibiting advantageous properties (low toxicity and anti-inflammatory effect), which can be further explored for COVID-19 treatment. Furthermore the epigenetic roles of the gut microbiome in aloe vera ingestion may play an important role for the prevention to COVID-19 and the targeting gut dysbiosis could help control the pathogenesis of COVID-19.

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