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Review Article

Adjuvanticity of Aloe Vera Gel and the Role of Butyrate Fermented as an Adjuvant for COVID-19 Vaccination

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Abstract

Adjuvants are added to vaccinations to boost their immunogenicity. We reviewed what we know about how butyrate affects immunity and adjuvant action. The usefulness of Aloe vera, aloe vera gel polysaccharide (acemannan), and butyrate fermented adjuvants in increasing Covid-19 immunization efficacy was thoroughly investigated. Butyrate, a known histone deacetylase inhibitor that stimulates expression of numerous genes involved in immune system pathways, was studied extensively for its adjuvanticity and effects on virus infection.

Keywords: *Adjuvanticity; Aloe Vera Gel; Butyrate Fermented; Covid-19 Vaccination*

Introduction

Various metabolites produced by commensal gut bacteria can mediate health advantages.

Acemannan, one of the metabolites butyrate produced from aloe vera gel polysaccharide, has been researched extensively as a commensal bacterium mediator. The gut microbiota is a diverse ecosystem. Thus, understanding the links between the gut microbiota and host immunity is critical for determining if therapies targeting the gut microbiota can increase vaccination or adjuvanticity efficacy. Aloe vera high molecular weight fractions as carbohydrate-based immune adjuvants were considered in a prior paper [1].

Intranasal immunization using hepatitis B surface antigen-acemannan formulations demonstrated the enhancement of the immune responses generating IgG antibody-titers in high level in mice serum [2,3]. Abdy., *et al.* [4] studied adjuvant effects of aloe vera gel in combination with formalin-killed *Aeromonas hydrophila* bacterin in immunization of common carp were evaluated and compared with Freund's adjuvant. The results showed that combination of *A. hydrophila* bacterin with adjuvant can improve the vaccine efficacy and resistance against *A. hydrophila* infection, and in comparison with traditional adjuvant (Freund's adjuvant), aloe vera gel could be used as a natural adjuvant with similar or even greater positive effects on vaccination of common carp. Song., *et al.* [5] explored the potential of orally administered aloe vera gel (acemannan) as an adjuvant for influenza vaccine in C57BL/6 mice. The mice were given a lethal homologous influenza challenge to test its adjuvanticity with a split-type pandemic H1N1 (pH1N1) Ag. pH1N1 aloe vera gel dosing orally Alum and MF59, which are already employed as adjuvants in influenza vaccine formulation, boosted survival rates in mice to levels close to those of alum and MF59. According to the findings, aloe vera gel could be utilized as an adjuvant for influenza vaccine. Yakabe., *et al*. [6] explored how the gut microbiota influences immunity and the interaction between gut microorganisms and trained innate immunity, vaccines, and adjuvants, as well as the immunological processes of vaccines and adjuvants.

The adjuvanticity of aloe vera gel and butyrate fermented to improve the efficiency of COVID-19 immunization was discussed in this paper.

Commensal bacterial metabolite, short chain fatty acids and the attenuation of pathobiont- induced hyper-inflammation by butyrate

Influenza A virus causes a severe respiratory tract illness, which is a major worldwide health issue. The crosstalk between the lungs and the gut is disrupted by influenza infection. Lu., *et al.* [7] conducted an *in vivo* study in which mice were given Lactobacillus mucosae 1025 and Bifidobacterium breve CCFM1026, as well as a mixture of the two bacteria, for 19 days. Probiotics were tested for their effects on clinical symptoms, immunological responses, and gut microbial changes. Butyrate was positively connected to MixA (an interferon-induced antiviral protein) expression but negatively related to viral loads, according to the correlation analysis. MixA lowered viral loads and enhanced the antiviral protein MxA expression, which was strongly connected with increased butyrate generation as a result of gut microbial change, according to the findings.

Various metabolites produced by commensal gut bacteria can mediate health advantages.

Butyrate has been explored as a mediator of commensal microorganisms, particularly SCFAs.

The beneficial metabolites may be deficient in COVID-19 due to dysbiosis, and Chen., *et al*. reported the use of butyrate to reduce the severity of COVID-19 infections [8]. The proposed use of butyrate by enema would achieve two goals: (i) direct application of butyrate to the site of the intestinal tract, terminal ileum, and right colon, which contains one of the highest concentrations of SARS-CoV-2 receptors, and (ii) increase butyrate absorption for systemic distribution, as the colon is the primary site for both production and absorption of butyrate [9]. The role of butyrate in reducing pathogenic bacterial-induced hyper-inflammatory responses was discussed [10].

The role of intestinal microbiota improving the efficacy of COVID-19 vaccination

Many vaccines against SARS-CoV-2 have now been created in order to elicit effective immune responses that will guard against SARS-CoV-2 infections or lower the severity of the disease if it is contracted. Many factors could influence vaccine efficacy in terms of achieving optimal immune responses. Because the gut microbiota is linked to the establishment and maintenance of an adequate immune system response, dysregulation of the gut microbiota (gut dysbiosis) could be a significant risk factor. Chen., *et al.* [11] addressed immunological responses to SARS-CoV-2, how COVID-19 vaccination elicit protective immune responses, the role of gut dysbiosis in vaccine inefficiency and side effects, and how functional foods can modulate the gut microbiota to promote COVID-19 vaccine immunization.

The use of probiotics as adjuvant therapy for COVID-19 management

In a recent study, we found that drinking aloe vera juice increases the concentration of the butyrogenic microbiota, *Faecali bacterium* spp., in the faeces, which may help with tissue repair [12].

With anti-inflammation, gut barrier strengthening, and butyrate generation, the intestinal symbiotic bacterium F. prausnitzii has emerged as the "sentinel of gut." F. prausnitzii may have the ability to avoid gastrointestinal comorbidities in COVID-19 patients by inhibiting inflammation [13,14].

To treat the virus's gastrointestinal effects in these patients, strategies to change the gut microbiome may be developed.

Adjuvant therapy for COVID-19 management using probiotics

A reduction in the severity and length of sickness could be beneficial not just to health systems around the world, but also to persons who are afflicted with COVID-19. Walton., *et al.* [15] looked at the relationship between the gut microbiota and COVID-19 infection and proposed theories for how probiotic and prebiotic interactions might work.

The use of probiotics as adjuvant therapy for COVID-19 management is one of interesting projects. A phase II trial applied the ozone therapy plus a probiotic's mixture to COVID-19 patients to prevent deterioration by Lau., *et al.* [16] in Italy (NCT04366089).

Metagenomics approaches to investigate the gut microbiome of COVID-19 patients

The current scientific knowledge and comprehension of the gut microbiota and COVID-19 interaction isn't perfect, but it's improving all the time. Archer., *et al*. found a decrease in beneficial commensals in COVID-19 patients [17]. One of these, *Faecali bacterium* prausnitzii, was shown to be lower in COVID-19 patients. *F. prausnitzii* has been identified as one of the major butyrate producers in the gut and plays a vital role in promoting gut health. Butyrate is important for the physiology of the intestines as well as the health of the host. Butyrate can minimize inflammation in the intestinal mucosa by inhibiting the activation in the intestinal mucosa by inhibiting the activation of NF-κB transcription factor, up-regulating PPARγ, and inhibiting IFN-γ. Sehli., *et al.* [18] suggested that understanding how to choose due to the computational tools and strategies to analyze efficacy the gut microbiota is one important thing to decipher the most pertinent microbiome profile for diagnostics and the precise antiviral or preventive microbial composition.

The potential adjuvant therapy of butyrate by enemas supportive treatment for patients with coronavirus SARS-CoV-2 infection

The estimated time from exposure to SARS-CoV-2 and the development of symptoms is about 5 days.

There is a significant change in intestinal microbial composition with reduced oral intake following the development of symptoms due to anorexia and other gastrointestinal disturbances (dysbiosis).

A drop in glucose fermentation and a subsequent decline in the formation of short chain fatty acids, most notably butyrate, are among the changes. Supplementing SARS-CoV-2 infected patients who can tolerate oral intake with microbial accessible and fermentable carbohydrates, according to Belkaid., *et al.* [19], could be a useful adjuvant in treating SARS-CoV-2 infection. For individuals who are unable to take food supplements or liquids by mouth, rectal butyrate delivery by enema may be considered. The proposed use of butyrate by enema would achieve two goals: (i) direct application of butyrate to the site of the intestinal track terminal ileum and right colon, which contains one of the highest concentrations of SARS-Cov-2 receptors, and (ii) increase butyrate absorption for systemic distribution, as the colon is the primary site for both production and absorption of butyrate. When delivered via enema, peros, or intravenously, butyrate treatment has been shown to be safe. The microbiota's adjuvant properties: function in infection and vaccine were described by the author [20] as follows: the microbiota may control the tissue milieu by maintaining a pool of commensal reactive cells with the ability to produce a heterologous adjuvant impact.

The triad association between gut microbiota, ACE-2 expression and vitamin D in COVID-19 severity

Articles from PubMed/Medline searches were reviewed by Shenoy [21], using a combination of terms: SARS-CoV-2, COVID-19, Inflammaging, Immune-senescence, Gut microbiome, Vitamin D, RAS/ACE2, and Vaccination. The author described that although there is hope that vaccinations may control COVID-19 pandemic eventually, the majority of global population is currently un-immunized, and it is too early to determine any long-term protective antibody levels and efficacy. This trinity, according to the author, may represent a significant link in determining the outcome of SARS-CoV-2 infection. Modulating these variables may have an impact on vaccine success and clinical outcomes in COVID-19 infections. In a previous review, we explored the significance of the gut microbiota during respiratory viral infections and proposed that using Aloe vera to target food supplements and gut dysbiosis could help manage the immunomodulatory effect in

COVID-19 pathogenesis [22]. We also discussed butyrate's potential role in intestinal homeostasis, as well as the effects of aloe constituents on the prevention of leaky gut syndrome, which is caused by increased intestinal permeability caused by ageing, which can lead to a variety of systemic inflammatory and immune-related dysfunctions [23]. Butyrate is a critical gut microbial metabolite that regulates the effects of the gut microbiota on the immune system. It not only plays a key role in maintaining intestinal immunological homeostasis, but it also has future therapeutic implications for a variety of gastrointestinal and systemic illnesses.

The mechanism of HDAC inhibition by butyrate and resulting alterations in the expression of genes involving in cell cycle, apoptosis, and transcriptional regulation

In bovine kidney epithelial cells, Li., *et al.* [24] discovered 450 genes that were strongly affected by butyrate. The findings shed light on how butyrate inhibits HDAC and causes changes in the expression of genes involved in cell cycle, apoptosis, and transcriptional control. Because butyrate regulates cell growth and proliferation as both a food and a signaling molecule, the findings in this study allow for a better understanding of the complete range of roles butyrate can play during cell development and proliferation.

Butyrate regulates COVID-19-relevant genes

Hypertension is one of the most common comorbidities with poor results, and it shares many pathophysiological aspects with COVID-19, such as inflammation and a malfunctioning renin-angiotensin system. Butyrate downregulates a gene required for SARS-CoV-2 infection, but it simultaneously upregulates the Toll-like receptor and other antiviral pathways, according to Li., *et al.* [25]. As a result, the higher incidence of COVID-19 in hypertension may be attributable in part to the gut's cumulative depletion of butyrate-producing bacteria. The author speculated that gastrointestinal butyrate control may play a role in COVID-19's greater comorbidity with hypertension.

Butyrate reprograms innate antiviral immune response mediated by type I interferon

Butyrate is a lipid produced by intestinal bacteria and a known histone deacetylase inhibitor that activates expression of many genes involved in immune system pathways. Chermudupati., *et al.* [26] investigated that butyrate reprograms the innate antiviral immune response mediated by type I interferons (IFNs). Many of the antiviral genes induced by type I IFNs are repressed in the presence of butyrate, resulting in increased virus infection and replication. Butyrate significantly suppresses the expression of specific antiviral IFN-stimulated gene by reprogramming the type I IFN-mediated innate antiviral infection of cells. The study found that gut microbiome metabolites like butyrate can have a variety of consequences on cellular physiology, including suppressing an inflammatory innate immune pathway, resulting in a proviral cellular milieu. (A provirus is an inactive form of a virus that is incorporated into a host cell's genetic material.) Because butyrate can raise virus titers in most circumstances, the author suggests that it could be used as a low-cost method to boost viral vaccine yields or study virus stocks. Treatment with butyrate or butyrogenic bacteria, which are increasingly being investigated for therapeutic purposes, should also be studied in terms of a balance of anti-inflammatory and proviral effects, according to the authors. By reprogramming the type I IFN-mediated innate antiviral immune response, butyrate inhibited the expression of particular antiviral IFN-stimulated genes, suggesting a new method by which butyrate impacts viral infections of cells. Butyrate reprograms the magnitude of induction for at least 63% of interferon-stimulated genes, identifying a new mechanism by which butyrate may affect virus infections.

Conclusion

The probable fermented metabolite from aloe vera gel is butyrate, a known histone deacetylase inhibitor that promotes expression of numerous genes involved in immune system pathways and has antiviral effects. It is important for maintaining intestinal immunological homeostasis and may have therapeutic implications for a variety of gastrointestinal and systemic diseases. Butyrate may have a wide range of effects on virus infection in cells. The efficacy of butyrate fermented in aloe vera gel as an adjuvant for Covid-19 immunization was thoroughly investigated.

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