OPINION article
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Could Nutraceutical Approaches Possibly Attenuate the Cytokine Storm in COVID-19 Patients?

Ramachandran Vignesh[1,2], Vijayakumar Velu[3*] and Sripathi M. Sureban[4*]

[1] Preclinical Department, Royal College of Medicine Perak (UniKL RCMP), Universiti Kuala Lumpur, Ipoh, Malaysia
[2] Infectious Diseases Laboratory, YR Gaitonde Centre for AIDS Research and Education (YRG CARE), Chennai, India
[3] Department of Pathology & Laboratory Medicine, Emory University School of Medicine, Division of Microbiology & Immunology, Yerkes National Primate Center, Atlanta, GA, United States
[4] Digestive Diseases and Nutrition Section, Department of Internal Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a colossal impact on public health, testified by being announced as a global pandemic by the World Health Organization (WHO) in March 2020. As of 1st April 2021, there have been over 128,223,872

confirmed cases of COVID-19 and over 2,804,120 fatalities reported by WHO (WHO Coronavirus Disease (COVID-19) Dashboard, 2021). Though COVID-19 vaccines are developed and being deployed around the world, considering the logistic challenges, vaccine-induced herd immunity is still a long way off (Vignesh et al., 2020). Despite being primarily a respiratory disease, mounting pieces of evidence point towards the impact of COVID-19 on the gastrointestinal system and the presentation of gastrointestinal (GI) manifestations (McDermott et al., 2020). In this opinion article, we summarize the effects of COVID-19 on the GI tract and also provide evidence of the role of nutraceuticals as a potential treatment strategy against COVID-19.

Coronavirus Disease 2019 (COVID-19) in Gastrointestinal Tract (GIT)

Coronaviruses, the single-stranded RNA viruses are spherical in shape and of their key structural components, are comprised of key structural components namely, the spike (S), envelope, membrane, and nucleocapsid proteins. Of these, the S protein remains the main determinant of pathogenicity being a requisite for viral entry into host cells. For the SARS-CoV-2 to gain entry into the host cell, it utilizes the receptor angiotensin-converting enzyme 2 (ACE2) and for S protein priming it uses the transmembrane serine protease 2 (TMPRSS2). Following entry, the replication of SARS-CoV-2 occurs in various cell types based on the expression of the ACE2 receptors such as in the lung cells, epithelial cells, enterocytes, and hepatocytes (Ferreira et al., 2020). Studies have revealed that the expression of ACE2 in the small intestine and colon is about 40x and 3x respectively higher relative to the lungs. Likewise, concerning the lungs, expression of TMPRSS2 is about 2x and 20x more in the small intestine and colon respectively (Cardinale et al., 2020; Zhang et al., 2020). Thus, the virus eventually produces and assembles new virions inside the cell which get released into the GIT. Studies have established the shedding of SARS-CoV-2 in the GIT even after the resolution of respiratory symptoms, underscoring the implications of GI infection. Albeit not as common as respiratory symptoms, GI symptoms like anorexia, nausea, vomiting, and diarrhea have been observed in patients with COVID-19. Meta-analysis studies have reported a pooled prevalence of GI symptoms among COVID-19 patients at about 18% (Cheung et al., 2020; Zhao et al., 2020). GI symptoms are observed to be associated with inflammatory processes leading to intestinal damage. Studies have revealed that by causing ACE2 modifications, SARS-CoV-2 infection in the gut could lead to gastrointestinal inflammation and other manifestations like diarrhea (Hoffmann et al., 2020). A study has demonstrated the role of SARS-CoV-2 infection in inflammatory reactions in the GIT as evidenced by diarrheal symptoms, increased levels of fecal calprotectin (FC), and a systemic IL-6 response (Effenberger et al., 2020).

The paramount role of the mucosal immune system has been implicated in the pathogenesis of COVID-19 at several levels (Russel et al., 2020). The secretory IgA antibodies have a key role in the protection of mucosal surfaces in the lung and gut from pathogenic viruses *via* various mechanisms. Recent findings suggest the predominance of secretory IgA antibodies in SARS-CoV-2 specific early humoral responses and these IgA antibodies have also exhibited relatively better-neutralizing activity than that of IgG (Sterlin et al., 2021). Interestingly, very high titers of SARS-CoV-2-specific IgA have been observed to correlate with the severe acute respiratory syndrome (Cervia et al., 2021). Also, significantly higher titers of IgA with potent neutralizing ability have been observed among COVID-19 patients with gastrointestinal symptoms indicating the key role of IgA (Wang et al., 2021). With mounting evidence from studies demonstrating the cross-talk between the lungs and gut microbiota, secretory IgA could be a significant mediator of this 'gut-lung axis' (Sencio et al., 2021; Vignesh et al., 2021).

Pathogenesis Mechanisms of Cytokine Storm in COVID-19

Dysregulation of Renin-Angiotensin System (RAS)

Various studies have demonstrated that the modulation of systemic inflammation is caused by regulating the renin-angiotensin system (RAS) that includes the ACE2. Homeostasis of RAS-ACE2 is required for healthy conditions and an imbalance to this is observed in the diseased conditions including diabetes, hypertension, and cardiovascular disorders (Villapol and Saavedra, 2015; Hoffmann et al., 2020). Interestingly, downregulation of ACE2 levels in tissues is associated with the pathogenicity of the virus leading to an imbalance of positive and negative regulation of RAS (Dijkman et al., 2012). It is already known that ACE-2 receptor blockers have been known to be effective in the management of diabetes, cardiovascular diseases, renal, and metabolic disorders (Villapol and Saavedra, 2015; Garg et al., 2020). Reduced expression of ACE2 has been observed to be associated with various conditions such as hypertension, diabetes, and cardiovascular conditions, which are also associated with COVID-19 as comorbidities (Magrone et al., 2020). Studies have shown upregulation of RAS by SARS-CoV-2 thereby depleting ACE2 in cardiovascular patients (Villapol, 2020). Thus, in COVID-19, perturbation of RAS-ACE2 balance could worsen the inflammatory responses leading to severe COVID-19 outcomes in patients with pre-existing comorbidities. In addition to its role in intestinal inflammation, ACE2 also has a key effect on the composition of the intestinal microbiota (Cole-Jeffrey et al., 2015), thereby hinting at the possible link for perturbed gut microbiota in the severity of COVID-19 among patients with pre-existing comorbidities.

The Possible Role of Gut Dysbiosis and Associated Leaky Gut

Metabolites of gut microbial flora such as the short-chain fatty acids (SCFAs) play a significant role in