Journal of Food and Agriculture Research
Vol. 2, No. 2, 2022, pp. 95-113

URL: www.arfjournals.com
https://doi.org/10.47509/JFAR.2022.v02i02.02

COVID-19 and Gastrointestinal Infection: New Approaches for Disease Management

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Abstract: Severe acute respiratory syndrome 2 (SARS-CoV-2) is a global pandemic associated with acute respiratory conditions. Besides, COVID-19 infection is also associated with gastrointestinal symptoms. Although there is no specific treatment for SARS-CoV-2 and a large section of the population worldwide is still not fully vaccinated, preventive measures and alternate supportive therapies have a significant role to play in the prevention and spread of the infection. This article summarises the features of SARS-CoV-2 infection in the gut and the role of the gut-lung axis toward host immunity. It also discusses the role of immunity-boosting foods, plant-based traditional herbs, and various probiotics and their mode of action against viral infection. Functional foods, nutraceuticals, and natural products can strengthen the immune system and also assist in fighting a viral infection. They contain immune-boosting components such as alkaloids, polyphenols, terpenoids, vitamins, minerals, and trace elements. Fruits, vegetables, probiotics, herbs, and fermented foods contain antiviral properties.

Keywords: COVID-19, gut-lung axis, immune response, cytokine storm, gastrointestinal tract.

Received : 10 July 2022
Revised : 09 August 2022
Accepted : 20 August 2022
Published : 30 December 2022

TO CITE THIS ARTICLE:

Aditi Sharma & Deepali Singh. 2022. COVID-19 and Gastrointestinal Infection: New Approaches for Disease Management. *Journal of Food and Agriculture Research,* 2: 2, pp. 95-113. *https://doi.org/10.47509/JFAR.2022.v02i02.02*

1. Introduction

The spread of the potentially lethal disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially reported in Wuhan, China, was declared a pandemic by WHO in March 2020 and named coronavirus disease 2019 (COVID-19) (Musa, 2020). Genome sequence information revealed that SARS-CoV-2 is a positive-sense single-stranded enveloped RNA virus, belonging to the β-coronavirus genus. Other members of this genus are SARS-CoV, MERS-CoV, human coronaviruses (HCoV), and in bat SARS-related

coronavirus. The bat coronavirus RaTG13 shares more than 93% sequence identity with the spike (S) gene of SARS-COV2 (suggesting that batCoV and human SARS-CoV-2 share a common ancestor), while the rest shares less than 80% sequence identity (Lan *et al.* 2020).

The coronavirus envelope consists of homo trimeric spike (S) glycoprotein which comprises two S1 subunits that determine the virus-host range and cellular tropism and a single S2 subunit that mediates virus-cell fusion of each spike monomer (Yuan *et al.* 2017). SARS-CoV-2 enters its host cell through the angiotensin-converting enzyme-2 (ACE-2) receptor, similar to SARS-CoV, and uses the cellular transmembrane protease serine 2 (TMPSS-2), which cleaves the S protein of human coronavirus, for priming activities (Hoffmann *et al.* 2020). Upon binding with the receptor's N-terminal, it induces the detachment of the S1 subunit of coronavirus with ACE-2 receptor through host TMPSS-2 to expose the C-terminal of the S2 subunit and stimulate S2 to transform from less stable (pre-fusion state) to more stable (post-fusion state) (Lan *et al.* 2020). This is an essential step for membrane fusion and invasion of the SARS-CoV-2 in the host cell. Once inside the host cell, the viral RNA is translated. After viral RNA replication and assembly, the virion-containing vesicles fuse with the host cell membrane resulting in the release of new viruses in the host (Guo *et al.* 2020).

Human coronaviruses are known to cause respiratory and enteric symptoms (Pan *et al.* 2020). During the SARS outbreak of 2002-03, 16%-73% of infected patients developed diarrhoea within the first week of illness (Zhang *et al.* 2020). COVID-19 patients have also shown similar respiratory symptoms such as fever, cough, dyspnoea, and pneumonia, while few also showed gastrointestinal (GI) symptoms such as diarrhoea, nausea, and vomiting (Pan *et al.* 2020). Several case studies have also reported patients developing GI symptoms much earlier than respiratory symptoms (Zhang *et al.* 2020, Wong *et al.* 2020, Jin *et al.* 2020, Malfertheiner *et al.* 2020, Ng and Tilg, 2020).

Single-cell transcriptomics studies have revealed that the ACE2 and TMPRSS2 are co-expressed in lung alveolar type 2 (AT2) cells upper epithelial cells in the oesophagus, gland cells, and absorptive enterocytes in the ileum and colon (Zhang *et al.* 2020). The presence of the receptors in the absorptive enterocytes of the digestive system could be one of the possible reasons for viral invasion in the digestive system. Additionally, the presence of SARS-CoV-2 in the digestive tract helps it in long-term existence in the human body even after the clearance of the respiratory tract. Wu et al. 2020 have reported the presence of SARS-CoV-2 RNA in the faecal samples for 11 days consecutively even after testing negative in the respiratory tract samples. The gut and lung axis

play an important role in the immune response against infections. Foods that strengthen the gut microbiome can act as supplements during the treatments of the patients and as a preventive measure for the healthy population. In this review, we have summarized the immune response by the body during the COVID-19 infection and the role of the gut-lung axis in the development of immunity, the effect of the immunity-boosting foods on the restoration of the gut microbiome, and the effect of active compounds found in the functional foods on SARS-CoV2 infection.

2. Immune Response and Cytokine Storm

In response to a viral infection, the host activates an immune response leading to the production of chemokines and immune mediators in infected cells. The viral infection is detected by pattern recognition receptors (PRR) by recognizing pathogen-associated molecular patterns (PAMP) in the viral RNA.

Dendritic cells are known to interfere with the viral particles and inhibition of the immune response possessed by them leads to the invasion of the virus (Li *et al.* 2020). T cells also have a role in eradicating the virus from the host (Mescher *et al.* 2006). CD8+ cytotoxic T cells can kill the virus-infected cells by secreting a range of molecules such as IFNγ, perforin, and granzyme, thereby limiting the spread of local infection. CD4+ helper T cells enhance the production of virus-specific antibodies by initiating T-dependent B cells and cytotoxic T cells (Diao *et al.* 2020; Neurath, 2020). Immune homeostasis is maintained by regulatory T cells by quelling the activation, differentiation, and pro-inflammatory function of lymphocytes such as B cells, NK cells, CD4+ T cells, and CD8+ T cells (Tufan *et al.* 2020). Coronavirus-infected patients show both innate and adaptive responses (Li *et al.* 2020). There were several reports of infiltrating plasma cells and lymphocytes in lamina propria of the stomach, duodenum, and rectum with intestinal edema seen in COVID-19 patients representing activation of immune cell response (Xiao *et al.* 2020). The hyper and hypo contractility of infected intestinal smooth muscle through calcium channels and G protein-coupled receptors is caused by Th1 and Th2 cytokines (Kopel, 2020). The viral infection leads to an increment in lung-derived CCR9+ CD4+ T cells. With the assistance of chemokine ligand (CCL25), CCR9+ CD4+ T cells are recruited into the small intestine which destroys the equilibrium of the gut microbiota affecting the immune system (Stenstad *et al.* 2006). This promotes the polarization of Th17 cells and enhances the production of IL-17A, leading to more damage to intestinal immunity as well as the development of gastrointestinal symptoms (Crowe *et al.* 2009).

In COVID-19 patients, a decrease in NK cells percentage, cytotoxic suppressor T cell (CD3+, CD8+), helper T cell (CD3+, CD4+), and regulatory T cells have also been reported, however, no change in B cells population was observed (Neurath, 2020; Tufan *et al.* 2020). A high percentage of severe COVID-19 patients, develop lymphocytopenia (low lymphocyte count), higher D-dimer, high blood urea, high creatinine, elevated neutrophil count, increased neutrophil/lymphocyte ratio, a lower percentage of monocytes, eosinophils, and basophils (Qin *et al.* 2020). Genetic variations have also been observed in tyrosine kinase 2 (TYK2, which provokes immune cells for the more inflammatory response), dipeptidyl peptidase-like protein 9 (DPP9, which plays a key role in inflammation), 2′-5′-oligoadenylate synthetase 1 (OAS, which helps to stop the virus from multiplying) and interferon-α receptor 2 (IFNaR2, which leads to low production of interferon) and hence allowing the virus to replicate rapidly. These findings demonstrated the reason why some people with coronavirus had no symptoms and others got extremely ill (Pairo-Castineira *et al.* 2020). Expression of some immune inhibitory factors on the surface of T cells such as PD-1 and Tim-3 was also observed in COVID-19 patients (Diao *et al.* 2020).

Cytokine storm is a deregulated immune response in which a huge amount of cytokines are produced in response to infection. The plasma of the COVID-19 ICU patients has shown increased levels of interleukins, colony-stimulating factors (granulocyte-CSF, granulocyte-macrophage- CSF), interferon (IFNγ), tumor necrosis factor (TNF α), macrophage inflammatory protein (MIP-1α, MIP-1β), and growth factors (fibroblast-GF, vascular endothelial-GF, platelet derived-GF) in comparison to non-ICU patients suggesting that cytokines play a vital role in the severity of disease (Gao *et al.* 2020). The induced cytokine burst can further cause damage to different organs such as the heart, liver, and kidney, and may lead to multiple organ dysfunction syndromes in severe cases (Neurath, 2020; Tufan *et al.* 2020).

3. Involvement of Gastrointestinal (GI) Tract

The viral replication in the gastrointestinal (GI) tract increases the severity of the disease leading to a longer time in the clearance of the virus from the host (Budden *et al.* 2017). It has been reported that COVID-19 patients having GI symptoms showed more severe disease conditions, increased aspartate transferase in the liver causing serious injury, haemoptysis, higher muscle ache, and increased complication of ARDS (Acute Respiratory Distress Syndrome) in comparison to patients without GI symptoms (Jin *et al.* 2020). Zhao *et al.* (2020)

reported the presence of SARS COV-2 nucleocapsid protein in the cytoplasm of the gastric, duodenal, and rectal epithelium highlighting the presence of the virus throughout the GI tract. Various clinical studies have reported the presence of gastrointestinal symptoms such as diarrhoea, nausea, or vomiting along with fever and other lung-related complications (Wang *et al.* 2020, Su *et al.* 2020; El Ouali *et al.* 2021).

The proximal and distal enterocytes in the intestine have higher ACE-2 expression that leads to direct exposure to foreign pathogens ingested with food. The interaction between ACE-2 receptors and SARS-CoV-2 results in the invasion of the virus which activates the enteric nervous system, edema, malabsorption, disturbed intestinal secretion, and finally diarrhoea (Zhang *et al.* 2020). A chain of inflammatory responses causes unintended damage to the digestive system (Pan *et al.* 2020). Recent studies have reported an increase in gamma-glutamyl transferase and alkaline phosphatase levels (Zhang *et al.* 2020), unusual levels of aspartate aminotransferase and alanine aminotransferase, and a moderate increase in serum bilirubin (Wong *et al.* 2020). Inflammatory cytokine storm, virus-induced cytopathic effects, an immune-related injury, and drug hepatotoxicity could be the cause of liver damage (Li *et al.* 2020). Alternatively, alterations in intestinal microbiota may also have a mutually intense effect on the lungs called a gut-lung axis (Budden *et al.* 2017).

4. Gut-Lung Axis and Microbiome Immunity

The establishment of gut microbes begins from birth and keeps on changing until a steady state is achieved which is nearer to adult micro-biota (Anand and Mande, 2018). In a healthy individual, the gut microbes are comprised of phyla *Actinobacteria, Bacteroidetes, Firmicutes, Verrucomicro-biota,* and *Proteobacteria* whereas the lung microbes consist of *Firmicutes, Bacteroidetes,* and *Probacteria* (Dhar and Mohanty, 2020, Bingula *et al.* 2017). Microbes and their host are in a symbiotic relationship (Ahlawat *et al.* 2020) and disruption of this balance often leads to diseases. The diversity of intestinal microbes decreases with age and this imbalance is called gut dysbiosis and often leads to inflammation and decreased immunity (Aleman and Valenzano, 2019). The higher susceptibility of the elderly and co-morbid population towards COVID-19 infection along with higher severity of symptoms and lung-related complications hint towards the gut-lung axis (Dhar and Mohanty, 2020). The gut-lung axis shows bi-directional interaction through the bloodstream, which is thus capable of modifying immunity (Conte and Toraldo, 2020). SARS-CoV-2 can affect the gut microbiota by travelling in the bloodstream from the lungs to the gut.

Translocation of surviving microbes by antigen-presenting cells (APC) to the mesenteric lymph node takes place within the lamina propria, then these microbes enter the circulation system, which further leads to pulmonary circulation and activation of DC, macrophages, and priming activities of naïve B and T cells (Anand and Mande, 2018, Bingula *et al.* 2017).

Coronaviruses are known to cause lung-related complications such as pneumonia and SARS-COV2 also induce a strong immune response termed a cytokine storm (Diao et al. 2020). Viral infections make the immune system secrete proinflammatory cytokines which cause changes in the gut microbiota resulting in dysbiosis and increased gut permeability (Wu and Wu, 2012). Leaked antigens and toxins enter the systemic circulation, leading to sepsis and multiple organ failure in COVID-19 patients. The massive use of antibiotics also results in dysbiosis and can cause antibiotic-associated diarrhoea (Wei *et al.* 2020). The bacterial translocation from the gut to the lungs has been reported in sepsis and acute respiratory distress syndrome (Dickson *et al.* 2016), possibly due to dysbiosis in gut microbiota (Fanos *et al.* 2020). Moreover, infectious viruses could translocate from infected lungs to distant organs via systemic circulation. In situ hybridization and electron microscopy studies on the infected patients as well as on autopsies of dead patients showed immune cells positive with viral sequences suggesting that the immune cells infected by the viruses could circulate and invade the enteric cells resulting in gastrointestinal damage. These results suggest that the coronavirus could translocate to systemic circulation after damage in lung tissue and migrate to intestinal cells through the circulatory and lymphatic systems (Gu *et al.* 2005). Thus, we cannot rule out the role of gut-lung microbiota in the pathogenesis of coronaviruses (Aktas and Aslim, 2020).

The gut microbes secrete different metabolites and immune-modulatory signals that contain short-chain fatty acids (SCFA) like acetate, propionate, and butyrate (Rooks and Garrett, 2016). SCFA has a wide variety of functions which are the maturation of immune cells, energy source, binds to G-protein which sense metabolites leading to the anti-inflammatory effect, production of antibodies like IgM and IgA, development of DC and inflammatory cytokines, and activation and differentiation of B cells (Kim *et al.* 2016). The increased production of SCAF helps in reducing pathogenic microbes like *Escherichia coli and Enterobacteriaceae,* as an increase in butyrate level promotes mucin production which decreases bacterial adhesion as well as lowering of pH in the gut (Zimmer *et al.* 2012). The major genus which produces SCFA is *lactobacillus, Clostridium, Prevotella, Bacteroides, Propionibacterium, Bifidobacterium,* and *Roseburia* (Macfarlane and

Macfarlane, 2012). Nutrition also plays a crucial role in the diversification, development, and composition of the microbiota. A diet rich in fiber influences gut as well as lung microbiota, recommending the influence of nutrition intake on the immunity of the lungs (Conte and Toraldo, 2020). When a high fiber-rich diet was given to mice, it has been found that there was an increase in SCFA level in blood which leads to higher protection against lung allergic inflammation, and changes in intestinal and lung microbiota were observed (Trompette *et al*. 2014). The use of probiotics shows improved results in inflammatory conditions and managing innate immunity using TLR and other correlated signaling pathways (West *et al.* 2017). In the gut, the probiotics are predominantly referred to as genera *Bifidobacterium* and *Lactobacillus.* Probiotics such as yogurt have shown an efficient decrease in the number of enteropathogens such as *Helicobacter pylori* and *E.coli* (Dhar and Mohanty, 2020). When the intestinal mucosa and micro-flora are unstable, this situation induces a high frequency of a virus infecting through this pathway. Investigations have approved that probiotics can treat diarrhoea. Specifically, lactic acid bacteria and bifidobacteria stimulate the production of antiviral antibodies which further enhances the removal of the virus from the host. *Lactobacillus plantarum* has a wide variety of immunomodulatory activity, particularly upon the infection of seasonal and highly pathogenic influenza viruses. Oral administration of *L. plantarum* in mice has been shown to alleviate inflammation and enhance immune response (Park *et al.* 2013; Kikuchi *et al.* 2014). These findings suggest that *L. plantarum* strengthens many aspects of the host defense mechanism against viral infection. Therefore, it is recommended to use probiotics for patients having diarrhoea induced by SARS-CoV-2 (Ye *et al.* 2020; Gao *et al.* 2020).

5. Functional Foods and COVID-19 Treatment

The ongoing treatment of COVID-19 patients is based on symptomatic and supportive care which includes the usage of analgesic drugs to reduce pain, antipyretic drugs to reduce fever, antibiotics, glucocorticoids, and oxygen therapy if required by patients (Su *et al.* 2020; Kopel, 2020). There are over 125 vaccine candidates across the globe from different institutions and manufacturers; they use six basic principles in vaccine preparation that is the use of a live attenuated virus, inactivated virus, nucleic acid: DNA and RNA, recombinant protein subunit, replicating viral vectors and non-replicating viral vectors (e.g. adenoviral vectors) (Pagliusi *et al.* 2020). Many drugs have been repurposed for the treatment such as Chloroquine (CQ) and hydroxychloroquine (HCQ) prevent virus-cell entry by blocking the glycosylation of ACE-2 cell receptors

and inhibiting the viral/cell fusion by blocking the endosomal trafficking and increasing the pH (Chen *et al.* 2020). Remdesivir and Favipiravir are adenosine and guanosine nucleotide analogue, respectively, which inhibit viral RNA polymerases and have been used for the treatment. Lopinavir, a well-known protease inhibitor, is used with ritonavir as a booster.

For the treatment of COVID-19 patients with GI symptoms, are recommended a balanced electrolyte rehydration therapy to maintain their hydration level, loperamide drug for antimotility, montmorillonite powder or probiotics, and antiviral such as oseltamivir and abidol are prescribed. Prochlorperazine and ondansetron are recommended for COVID-19 patients having nausea and vomiting (Su *et al.* 2020; Ouali *et al.* 2020).

Functional foods are dietary items with dual roles of providing nutrition energy along with immunity-boosting qualities (Martirosyan and Singh, 2015; López-Varela *et al.* 2002). Multiple studies have reported the use of prebiotics, probiotics, and ayurvedic products as natural boosters of the immune response. These food components help to maintain gut health by maintaining the commensal relationship with microflora and bacterial colonies in the gut (Singh *et al.* 2020). Micronutrients, probiotics, flavonoids, carotenoids, and herbs have been reported beneficial to immune health, and deficiency of micronutrients has been linked to a weak immune system (Maggini *et al.* 2018).

Traditional medicines, herbal plants, and their products are also considered as one of the treatments because of their antiviral, anti-inflammatory, antipyretic, and immune booster properties- and target different viral proteins. ACE2 inhibitors can be a good candidate for potential therapy and screening of medicinal plants demonstrating that *Rheum officinale* and *Polygonum multiflorum* could inhibit ACE2 receptors. The extracts also inhibited the S protein and ACE2 interaction in a dose-dependent manner (Ho *et al.* 2007) *Aconitum carmichaelii*, *Glycyrrhiza glabra,* and *Zingiber officinale* decrease the expression of ACE2 receptors in the lung tissue (Liu *et al.* 2018). Other viral enzymes that are important for viral replication are 3C-like protease (3CLpro), papain-like protease, helicase, and RdRp. Natural inhibitors of these enzymes can act as potential candidates for COVID-19 treatment. Tannins from *Camellia sinensis* are potent inhibitors of 3CLpro (Chen *et al.* 2005). Papain-like-protease is inhibited by the bioactive compounds present in *Salvia miltiorrhiza*, *Alnus japonica,* and *Curcuma longa* (Park *et al.* 2012). Naturally occurring inhibitors of RdRp can be found in the extracts of *Dacrydium araucarioides* (Coulerie *et al.* 2013). Extracts from *Aglaia silvestris* and *Faviolata* contain potent inhibitors of viral helicase (Müller *et al.* 2018).

Various terpenoid derivatives such as glycyrrhiza from *Glycyrrhiza glabra* (Cinatl *et al.* 2003); quinone-methide triterpenes from *Tripterygium regelii* (Ryu *et al.* 2010); tanshinones from *S. miltiorrhiza* (Park *et al.* 2012); triterpenoids from *Euphorbia neriifolia* (Chang *et al.* 2012) have shown potent antiviral activities against coronaviruses and have potential for being effective against COVID-19.

Similarly, polyphenols such as resveratrol (from *Vitis vinifera*, *Vaccinium macrocarpon*, and *Polygonum cuspidatum*); luteolin and quercetin derivatives (Chen *et al.* 2006); Baicalin (glycosylated flavonoid from *S. baicalensis* (Chen *et al.* 2004) can be promising antivirals against COVID-19. Alkylated chalcones and diarylheptanoids such as curcumin are polyphenols that also show potent inhibitory activity against viral proteins (Park *et al.* 2012) and could be a candidate for COVID-19 prevention and treatment. Alkaloids and derivatives such as lycorine from *Lycoris radiata* and emetine from *Carapichea ipecacuanha* have shown strong inhibition of viral replication against MERS, HCoV-OC43, HCoV-NL63 in in-vitro studies (Li *et al.* 2005; Shen *et al.* 2019). Tylophorine from *Tylophora indica* can target viral RNA replication and block the pro-inflammatory response of host cells in CoV infection (Yang *et al.* 2017). *Armeniacae semen* herb inhibits immune response by inhibiting Th2 cells (Do *et al.* 2006). This herb has been suggested for the therapy of pediatric COVID-19 patients with mild symptoms. When *Armeniacae semen* and *Coicis semen* are given together, they enhance the treatment of upper respiratory infection (Xi and Gong, 2017). Molecular docking analysis of some natural products like glycyrrhizin, rhein, berberine, and tryptanthrin have shown the highest degree of interaction with SARS-CoV-2 viral protease indicating the constructive integration inside the protein pocket making them an effective candidate to obstruct SARS-CoV-2 viral protease (Narkhede *et al.* 2020). *Glycyrrhizae radix* is a medicinal plant highly recommended for the treatment of adult COVID-19-affected patients (Ang *et al.* 2020). A few other medicinal plants with pharmacological and biological action against SARS-CoV-2 infection have been recommended for treatment and are listed in [Table 1].

Table 1: Potential plants, their active compounds, and mechanism of action against SARS-CoV-2

S. No	*Plant Name*	*Active Compound*	*Mechanism of Action*	*Reference No.*
1.	*Glycyrrhizae radix*	Glycyrrhizin	Inhibit viral adsorption, penetration, and entry.	Cinatl *et al.* 2003
2.	*Panax ginseng* *Aesculus hippocastanum* Rauwolfia genus	Ginsenoside Rb-1 Aescin Reserpine	Inhibited replication of virus at non-toxic concentration.	Wu *et al.* 2004

3.	*Scutellaria baicalensis* *Veronicalina riifolia* Rheum and Polygonum genus	Baicalin Luteolin Emodin	Inhibit interaction of SARS virus S-protein with Ace-2	Chen and Nakamura, 2004; Yi *et al.* 2004; Hoty *et al.* 2007
4.	*Khaya grandifoliola* *Allium cepa* *Tripterygium regelii* *Isatis indigotica* Torreya nucifera	6-Acetylswietenolide (terpenoid) Quercetin Celastrol, Pristimerin α-sitosterol Amentoflavone	Inhibits coronavirus chymotrypsin-like protease.	Ryu *et al.* 2010; Gyebi *et al.* 2020; Mani *et al.* 2020; Ryu *et al.* 2010
5.	*Curcuma longa* Fragaria ananassa	Curcumin Fisetin	Interacts with the C-terminal of S1 and S2 domains of spike protein and blocks the site for further viral attachment.	Pandey et al. 2020
6.	*Echinacea purpurea*	Cichoric acid, polyacetylenes, and alkamides	Induces the production and secretion of cytokines (IL-1, IL-10, TNF-a, and IFN-a)	Kim *et al.* 2014; Bodinet and Beuscher, 1991
7.	*Psoralea corylifolia*	Bavachinin	Inhibition of papain-like protease	Binns *et al.* 2002
8.	*Zingiber officinale* *Allium sativum* *Echinacea* *Garcenea kola* Olea europaea	Gingerol Allicin Caffeic acid Kolaviron Oleuropein	Blocking viral RNA-dependent RNA polymerase and chymotrypsin-like protease activity.	Bc *et al.* 2020

6. Conclusion

The outbreak of COVID-19 has spread all over the globe in a very short duration. Predominantly, the infection of SARS-CoV-2 affects the respiratory tract but its manifestation was also observed in the intestinal tract and the common GI symptoms are diarrhoea, nausea, and vomiting. SARS-CoV-2 affects the host cell through entry by ACE-2 receptor and TMPSS-2. The infection causes indirect damage to the liver leading to a high level of aspartate and alanine transferase. Recognition of the SARS-CoV-2 genomic RNA or other viral particles (PAMP) by the PRRs such as TLR and RIG-I led to a cascade of immune responses, thereby triggering the release of a huge amount of cytokines and chemokines. The gut-lung axis plays a crucial role in enhancing immunity and disruption of the gut barrier due to dysbiosis could also be the cause of the translocation of CoV-2 to the intestine. Also, a decrease in the diversity of gut microbiota with age or because of the intake of medications for various health conditions could contribute to the severity of COVID symptoms in the older population.

Dietary habits and supplements could play a crucial role. A high-fiber diet that enhances SCFA production by gut microbes, as well as the use of probiotics, can help in a better immune response against diseases. The immune-boosting nature of prebiotics, probiotics, herbs, and flavonoids can be used as an alternate treatment for the prevention and treatment of COVID-19. Functional foods, natural products, and nutraceuticals have been used to enhance the immune response and can be promising candidates in the treatment of COVID-19. Many superfoods, herbal medicines, and probiotics can improve the immune response and be useful in COVID-19 treatment and prevention. These foods can inhibit coronavirus in different stages of the viral life cycle. In vitro molecular docking studies have identified many promising candidates. Finally, a better understanding of the gut-lung axis and viability of COVID-19 transmission via faeces should be studied extensively for the understanding of the disease spread especially through asymptomatic patients. Advanced studies are also needed to validate the efficacy of the *in-silico-identified* active compounds derived from food. Further analysis needs to be carried out for standardized use of all the superfoods for effective treatment against corona.

Funding (information that explains whether and by whom the research was supported) – Work in DS lab is supported by DBT-BIOCARE and SERB fund

Conflicts of interest/Competing interests (include appropriate disclosures) – None

Ethics approval (include appropriate approvals or waivers) – NA

Consent to participate (include appropriate statements) – NA

Consent for publication (include appropriate statements) – NA

Availability of data and material (data transparency) – NA

Code availability (software application or custom code)- NA

Author and co-author contribution- The idea was conceived by DS, and was written by AS and proofread by DS

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Figure 1: When SARS-CoV-2 invades the host cell with the help of the ACE-2 receptor and TMPRSS2, the viral ssRNA is recognized by different pattern recognition receptors like RIG-1, TLR-2, TLR-7, and TLR-8 present at various location in a cell. If the viral RNA is recognized by RIG-1, it further stimulates the IPS-1 present on the mitochondrial surface leading to the production of NF-kB, IRF-3, and IRF-7 by TRAF-3. If the viral RNA is recognized by TLR's, they activate TiRAP which induces MYD88 and TRIF to produce NF-kB, IRF-3, and IRF-7. These NF-kB, IRF-3, and IRF-7 move inside the nucleus for the production of IL-1, IL-6, IFN-α, TNF-β, and other inflammatory cytokines. These cytokines are released outside the cell for further immune response. Outside the cell, mature dendritic cells provoke the activation of B cells, T cells, and natural killer cells which further enhances the immune response. (ACE-2: Angiotensin-converting enzyme; TMPRSS-2:Transmemberane protease serine-2; RIG-1: Retinoic acid-inducible gene-1; IPS-1: IFN-β promoter stimulator-1; TRAF-3: TNF receptor-associated factor-3; NF-kB: Nuclear factor kappa light chain enhancer of activated B cells; IRF: Interferon regulatory transcription factor; IL: Interleukins; IFN: Interferons; TNF: Tumor necrosis factor; TiRAP: Toll interleukin 1 receptor(TIR) domain-containing adaptor protein; MYD88: Myeloid differentiation primary response 88; TRIF: TIR domain-containing adaptor inducing interferon-β; iRAK-1: Interleukin-1 receptor-associated kinase; TLR: Toll-like receptor).