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COVID-19 and Diarrhea: Putative Mechanisms and Management

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Highlights

- Mechanism of diarrhea in COVID-19 is mainly associated with ACE2.
- Altered gut microbiota and side effects of medications can lead to diarrhea.
- Diversified medications are used to manage the complications.

Abstract:

Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of the coronavirus disease 2019 (COVID-19), has recently posed a threat to global health by spreading at a high rate and taking millions of lives worldwide. Along with the respiratory symptoms, there are gastrointestinal manifestations and one of the most common gastrointestinal symptoms is diarrhea which is seen in a significant percentage of COVID-19 patients.

Literature review: Several studies have shown the plausible correlation between overexpressed angiotensin converting enzyme 2 (ACE2) in enterocytes and SARS-CoV-2, as ACE2 is the only known receptor for the virus entry. Along with the dysregulated ACE2, there are other contributing factors such as gut microbiome dysbiosis, adverse effects of antiviral and antibiotics for treating infections and inflammatory response to SARS-CoV-2 which bring about increased permeability of gut cells and subsequent occurrence of diarrhea. Few studies found that the SARS-CoV-2 is capable of damaging liver cells too. No single effective treatment option is available.

Limitations: Confirmed pathophysiology is still unavailable. Studies regarding global population are also insufficient.

Conclusion: In this review, based on the previous works and literature, we summarized the putative molecular pathophysiology of COVID-19 associated diarrhea, concomitant complications and the standard practices of management of diarrhea and hepatic manifestations in international setups.

Keywords: COVID-19, SARS-CoV-2, Diarrhea, COVID-19 diarrhea, ACE2, Angiotensin Converting Enzyme, Diarrhea Management, Antibiotic Associated Diarrhea.

1. Introduction

Since December 2019, Coronavirus disease (COVID-19) has become a global threat to public health and economy. The main causative agent of this disease, SARS-CoV-2 had first appeared in Wuhan city of China and WHO declared it a global pandemic on March 2020 (Huang et al., 2020). Along with a great toll on economic growth and interruption of the general lifestyle of people, COVID-19 has become one of the major public health crises infecting around 533 million people till June 12 2022, and taking more than 6.3 million lives, reported from 226 countries ((WHO), 2022). But there is a probability that the number of the infected people and the deaths are much higher because of underreporting and receiving support from the practice of telemedicine (Abdel-Naser, 2021).

The causing agent of COVID-19, SARS-CoV-2, is a member of Coronavirus group and Nidovirale family. The main characteristics of the members of this family are , the spike-like structures of the viruses, the ability to spread swiftly and be converted into a new variant of concern and higher infectivity and mortality rates, which make this virus a novel one (Loo and Letchumanan, 2021). After the virus entering into the body via respiration, it affects the lung resulting in cough with sputum production, shortness of breath, and in severe cases, acute respiratory distress syndrome (ARDS), respiratory failure, and sometimes, even death (Mohamed et al., 2021). There are several other organs which are affected by COVID-19 and those extrapulmonary manifestations include cardiovascular disorders such as myocarditis, pericarditis, arrhythmias, acute coronary syndrome, and heart failure; renal disorders e.g., acute tubular necrosis. Along with these adverse effects on the organs themselves, hepatic dysfunctions are also seen in many patients and this may lead to elevated level of enzymes such as ALT, AST, and serum bilirubin. Also, some dermatological changes due to COVID-19 were also experienced by patients which include vesicles, maculopapular rashes, petechiae, purpura, urticaria, pernio, distal limb ischemia and livedo racemose (Gottlieb and Long, 2020). A significant number of people also experienced neurological symptoms such as cephalgia, peripheral neuropathy, encephalopathy, cerebrovascular disorders, and vertigo (Johnson et al., 2020). In general. the practice of telemedicine may have contributed to the underestimation of the true magnitude of the pandemic. (Abdel-Naser, 2021)

Though the key manifestations of COVID-19 patients were fever, and sometimes respiratory symptoms, many case reports showed different percentages of patients having gastrointestinal

symptoms and altogether the range varies from 2% to 79.1% (Guan Wei-Jie et al., 2020, Jin et al., 2020, Lin et al., 2020, Wang et al., 2020, Wang et al., 2021, Zhang Jin-Jin et al., 2020). These symptoms can emerge anytime during the COVID-19 infection, in beginning or after the onset of fever or even later. The most common gastrointestinal (GI) symptoms include diarrhea, lack of appetite, nausea, vomiting, and sometimes, abdominal pain (Gu et al., 2020). In severe cases, patients experience bleeding in the GI tract (GIT) (Wang et al., 2021).

Though diarrhea is the most common GI manifestation, the underlying causes are still unclear. As GIT manifestations are found in nearly one-fifth of COVID-19 patients (Henry et al., 2020), this article is going to offer insights into the GIT symptoms, associated mechanisms, and pathological changes caused by SARS-CoV-2 infection and provides an outline of current treatment options.

2. Pathophysiology and Mechanism of GIT Related Manifestations

2.1. Mode of Entry into Cell and Molecular Pathophysiology of Diarrhea

SARS-CoV-2 is the largest known RNA virus having a genome of 30kb in length and the RNA is single-stranded positive sense in nature. All known coronaviruses share a few common structural features. One of them is the structural proteins (SPs). There are four basic structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins and all of them are encoded by the viral genome (RNA) (Malik, 2020). These structural proteins play significant

roles in viral invasion into the host cells. The S-protein attaches to the host cell glycoprotein receptor, angiotensin-converting enzyme 2 (ACE2), initiating the whole process of infection. The shaping of virion particles and binding to nucleocapsid is the responsibility of the M-protein. E protein helps in the assembly and release of viral particles whereas N-protein aids the genome to bind to the treplication-transcription complex and to proceed the whole replication process.

It was believed that the SARS-CoV-2 virus enters into the host cell via two pathways. One is pH-dependent and another is pH-independent. In pH-independent pathway, the viral envelope gets fused with the membrane of the host cell and the genetic material is then delivered into host cell. On the other hand, the pH-dependent pathway, which is now established as the main mechanism of entry, uses a clathrin-mediated endocytic pathway involving the binding to the extracellular domains of ACE-2 receptors (Bayati et al., 2021, Hu et al., 2020). ACE-2 is a transmembrane metallopeptidase enzyme, found mostly on the plasma membrane of cells (Hamming et al., 2004). In the pH-dependent pathway, acidic pH stimulates the fusion of viral particles and endosomal membrane. After the formation of the endosome, the virion is activated and releases the genomic contents into the host cell cytoplasm for further replication process (Wang et al., 2008).

The spike of SARS-CoV-2 which initiates the process of endosome formation is a homotrimer composed of three similar copies of the same glycoprotein chain which are attached together. A spike has two structural subunits- S1 and S2. The S1 subunit contains a receptor-binding

domain (RBD) having a residue 394 (glutamine) (Shang et al., 2020) that can be recognized by the critical lysine 31 on the human ACE2 receptor (Wu et al., 2012). The S2 subunit, on the other hand, contains a transmembrane part of the spike protein and is crucial for fusing the viral membrane with the membranes of the host cell (Hoffmann et al., 2020, Letko et al., 2020). These two subunits are generally fused together but, after attaching to host cell ACE2 via RBD of spike protein, the spike is cleaved into S1 and S2 which is mediated by human cell-derived proteases such as furin, type II transmembrane serine protease (TMPRSS2), trypsin-like proteases, plasmin, elastase and factor Xa (Davidson et al., 2020, Hussain et al., 2020, Letko et al., 2020, Lippi et al., 2020, Walls et al., 2020, Wang et al., 2021, Wruck and Adjaye, 2020). Following segregation, the S1 subunit binds to ACE2, and the S2 subunit subsequently leads to the fusion of the viral membrane and the host cell membrane via a molecular mimic of soluble N-ethylmaleimide-sensitive factor protein receptor (SNARE)-mediated cellular membrane fusion, resulting in endocytosis (Hamming et al., 2004, Walls et al., 2020). When endocytosed, viral RNA enters the host cell and directs to the replication of the virus (Figure 1).

Several studies are showing that ACE2 is ubiquitous within the human body, expressed primarily on the luminal surface of epithelial cells, particularly overexpressed on the intestinal epithelial cells of the gut, smooth muscle cells and endothelial cells of blood vessels, lung, heart, brain, testis and renal tubular epithelial cell (Ortiz-Melo and Gurley, 2016, Patel et al., 2016, Turner et al., 2004, Zhang Haibo et al., 2020, Zhao et al., 2020), but under expressed on crypt of epithelial cells and in colon (Hashimoto et al., 2012). As COVID-19 symptoms are primarily respiratory tract oriented and in most of the cases, GIT related, and the presence of

ACE-2 receptors are high in there, it can be said that the virus infects and replicates within the GIT (Wong et al., 2020) resulting in COVID-19 associated diarrhea. One of the main basic body mechanisms that SARS-CoV-2 interrupts is the Renin-Angiotensin-Aldosterone System (RAAS). Principal functions of this system include elimination of oxidative stress, vasoconstriction and inflammation which are regulated by angiotensin II, one of the three components of RAAS. Two other components of this system are angiotensin-converting enzyme (ACE) and angiotensin receptor 1 (AT1R); angiotensin II exerts these effects after binding to AT1R (Obukhov et al., 2020). The ACE/angiotensin II/AT1R axis has pro-inflammatory and vasoconstrictive effects (Aksoy et al., 2020) and ACE2/ angiotensin (1-7)/Mas pathway downregulates this axis resulting in anti-inflammatory effects (Jia et al., 2009). After entering into cell, SARS-CoV-2 and ACE2 receptor both are internalized in the endolysosomal compartment and ACE2 receptor is being degraded there following the disruption of RAAS (Hoffmann et al., 2020, Letko et al., 2020, Zang et al., 2020). There is another enzyme named, 'A disintegrin and metalloprotease domain 17 (ADAM17)',which acts as sheddase and participate in shedding of ACE2, EGFR ligands and tumor necrosis factor-alpha (Xu Jincheng et al., 2020). When ADAM17 mediates the cleavage of ACE2, the level of ACE2 on the cell membrane drops and this phenomenon leads to pro-inflammatory effects by changing the balance of the ACE/angiotensin II/AT1R pathway (Megyeri et al., 2021).

Another mechanism involves two viroporins of SARS-CoV-2. One of them is the E protein which is a membrane protein forming a homopentameric ion channel. This ion channel shows selective permeability for monovalent ions like K^+, Na^+ and Cl^- and a bivalent ion, Ca^{2+} (Cao et

al., 2020). When the E proteins accumulate in the endoplasmic reticulum and Golgi membranes, they carry Ca^{2+} to the cytoplasm from these compartments. Elevated Ca^{2+} in cytoplasm can increase the rate of transportation of apical Cl^- outside of the cell through the Cl^- channel activated by Ca^{2+} (Barrett and Keely, 2000). Another protein is Orf3a, which is also an ion channel protein, that carries K^+ ions through viroporins, localized on plasma membrane and endomembrane (Figure1) (Ren et al., 2020, Xu Huanzhou et al., 2020). Primary function of Orf3a in the cytoplasmic membrane might be the leaking of K^+ ion from intestinal epithelial cells. This intracellular imbalance of multiple ions caused by these viroporins leads to activation of NRP3 inflammasome (NOD-, LRR-, and Pyrin domain-containing 3) resulting in secretion of interleukin (IL)- 1β, following cell death (Lin et al., 2020, Theobald et al., 2020). This IL- 1β then creates a local inflammatory environment by activating innate immune cells and thus, a systemic cytokine storm. Together, the indirect cytokine storm and the direct viroporin activation, trigger the ionic imbalance in enterocytes and finally leads to the occurrence of diarrhea (Megyeri et al., 2021).

The third possible mechanism of diarrhea involves an amino acid transporter named Broad Neutral Amino Acid Transporter 1(B_0AT1) which takes part in Na+- coupled transportation of tryptophan, glutamine, leucine and phenylalanine. ACE2 binds to B_0AT1 creating a heterodimer complex (Andring et al., 2020) and when SARS-CoV-2 attaches to ACE2: B_0AT1 complex, it can impair the transportation of Na^+ and neutral amino acid (Obukhov et al., 2020). As a consequence, amino acid starvation takes place which may reduce Na+ uptake leading to the development of diarrhea.

2.2. Altered Gut Microbiota

One of the most common characteristics of human intestine is the habitat of a large number of commensal microbes and the diversity is incredible, consisting of around 1000-1500 species. For instance, in the gastrointestinal system, colon has almost 33% of all the bacterial cells present in human body (Lee et al., 2021). Main roles of these large population of gut microbes are boosting the host metabolism, protecting the host against disease causing organisms by habitat colonization and immunoregulatory responses, also by developing and strengthening the host immune system and maintaining immune homeostasis (Iacob et al., 2019, Laville et al., 2019, Lee et al., 2021, Pan et al., 2020, Rodionov et al., 2019, Sharma et al., 2019, Shin et al., 2019)

When the normal population of gut microbiota is altered, it may affect the respiratory tract too through common mucosal immune system. Alternate situation can also take place where the respiratory tract microbes are compromised resulting in digestive tract related disorders caused by immunoregulation. Several factors can negatively influence gut microbes. Such factors include age, any disease, concomitant infections, overuse or premature termination of antibiotic uptake, and viral-induced inflammation resulting in high or low plasma concentration of proinflammatory mediators e.g., cytokines, chemokines, inflammation markers. Sometimes, probiotic strains (e.g., *Bifidobacteria*), which produce butyrate, a short chain fatty acid (SCFA) playing important metabolic functions and maintaining the integrity of intestinal epithelium, are lowered due to amino acid starvation. When these factors come individually or all together,

they lead to alterations in infection susceptibility and disease severity through dysbiosis of community structure and function (Mangiola et al., 2018, Perisetti et al., 2020, Xiang et al., 2020).

Another factor that affects the normal population of gut microbiota, is reduced serum level of neutral amino acids, especially tryptophan. ACE2 has functions other than initiation of viral entry into host cell which is regulating the amino acid homeostasis in intestine by transporting it there. Intestinal SARS-CoV-2 may influence tryptophan absorption by influencing the ACE2:B_0AT1 transportation complex. This influence further affects the mammalian target of Rapamycin (mTOR) which controls the presence of antimicrobial peptides. Reduced tryptophan level and the lowered expression of antimicrobial peptides, together can negatively affect gut microbial ecology leading to transmissible susceptibility to colitis (Hashimoto et al., 2012, Xu K. et al., 2020), intestinal inflammation and diarrhea (Figure 2). This leads to the speculation of an association between COVID-19 and the gut microbiota (Gao et al., 2020). Two of the most common gut bacteria are *Lactobacillus* and *Bifidobacterium* and they were found to decrease in some COVID-19 patients as well (Xu K. et al., 2020).

2.3. Side Effects of Medications Used to Treat COVID-19

Antiviral drugs, antibiotics, and corticosteroids are used in the treatment of COVID-19 patients (Megyeri et al., 2021) but there are possible side effects of these medicines. One of the major side effects is antibiotic-associated diarrhea which could also be mistaken as COVID-19 symptom. Depending on the time of onset of diarrhea, it could be early-COVID-19 associate

diarrhea and late-antibiotic associated diarrhea (Maslennikov et al., 2021). In case of first one, viral RNA is found in the stool sample depicting that it is caused by the virus itself and it is usually benign, self-limiting and the need for medical attention is limited. But, in the fecal sample of patients with late diarrhea, viral RNA was absent leading to the idea of antibiotic-associated diarrhea which could be fatal if untreated.

Antibiotics are not the treatment option for COVID-19 itself, but are administered for treating the secondary bacterial infection caused by frequently detected *Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae*, *Escherichia coli, Acinetobacter* spp. *Neisseria meningitides* and *Haemophilus influenzae* (Handel et al., 2009, Sharifipour et al., 2020) and the infection rate is higher in critically ill patients who are in intensive care unit (Pourajam et al., 2022) . The use of antimicrobial drugs can alter the normal intestinal microbiota leading to antibiotic associated diarrhea as mentioned earlier. They also affect antibody production and immune system which could prolong the clearance of SARS-CoV-2 from the gut (Perisetti et al., 2020). Another problem may arise if the patient is treated with broad-spectrum antibiotics, which leads to the possibility of *Clostridiodes difficile* infection (CDI), even long after recovery from COVID-19. When someone has both CDI and COVID-19, it damages the intestine more severely resulting in more severe GIT associated symptoms (Granata et al., 2020).

Antiviral drugs such as favipiravir and remdesivir which are RNA polymerase inhibitors, lopinavir and ritonavir, used to treat COVID-19 patients also caused diarrhea in some cases (Mifsud et al., 2019, Perisetti et al., 2020, Ye et al., 2020).

There is another treatment option which may cause diarrhea namely the use of monoclonal antibodies(mAbs) such as sarilumab, siltuximab and tocilizumab. The main purpose of these mAbs is to offset the effects of proinflammatory cytokines such as IL-6 by inhibiting the IL-6 receptors (Hanna et al., 2021).

2.4. Inflammatory Response to GIT and Bile Acid Diarrhea

One of the mechanisms by which SARS-CoV-2 damages the intestinal tract is via inflammatory response leading to diarrhea and the major causes of this 'inflammatory storm' are excessively released cytokines and immune dysregulation (Liu et al., 2020, Wu et al., 2020).

Intestinal inflammation may trigger COVID-19 associated diarrhea through some mechanisms including reduced reabsorption of secreted bile acids in the terminal ileum. Bile acids are major organic substances of bile which are absorbed in the distal small intestine and then return to the liver, re secreted from there which is known as enteropathic circulation. During this process, only 5% of the total bile acids are lost during defecation which means the process is precise (Ticho et al., 2019).

There is a bile acid absorption system on the apical epithelial surface of gut epithelia which is controlled by a sodium-dependent bile acid transporter (ASBT). In case of ileal inflammation, a lot of inflammatory cytokines are present and if, particularly, IL-6 is present, it decreases the expression of ASBT (Craddock et al., 1998, Ha et al., 2021, Lazaridis et al., 1997, Neimark et al., 2006, Shirohata et al., 2022) which leads to decreased bile acid absorption capacity at the distal ileum (Oelkers et al., 1997). As a result, bile acid in colon increases and this stimulates colonic water secretion and peristalsis, leading to bile acid diarrhea (Ticho et al., 2019).

3. Concomitant Complications and Underlined Factors

In addition to respiratory and GIT symptoms, SARS-CoV-2 can damage hepatocytes with subsequent hepatic dysfunction (15-78% of the cases) which results in increased ALP (4.6%), ALT (20.6%), AST (22.8%) and bilirubin (7.8%) levels and slightly reduced albumin (39.8%) level. (Zarifian et al., 2021).

It is hypothesized that the main reason behind COVID-19 associated liver injury is ACE-2, in other words, where the ACE2 receptors are present, COVID-19 associated pathogenesis will be present too. Upregulation of ACE2 is thought to be one mechanism of pathogenesis in liver tissues as a result of the hepatocyte regeneration in liver homeostasis (Pu and Zhou, 2022)The main function of ACE2 is to offset the vasoconstriction effect of angiotensin II, thus decreasing the liver damage through renin-angiotensin system (Paizis, 2005). But a recent study showed that ACE2 was highly expressed in hepatocytes and cholangiocytes suggesting the possibility of COVID-19 associated liver injury (Chai et al., 2020, Pu and Zhou, 2022). Another hypothesis suggests that the liver injury in COVID-19 might be due to a secondary injury from hypoxia which leads to a sharp increase of ACE2 in hepatocytes and bile duct cells (Paizis, 2005) and thus increased entry of the virus into the liver.

4. Management of COVID-19 Associated Diarrhea and Liver Injuries

COVID-19 associated diarrhea is mostly moderate or mild, so, it is often self-limiting. Drug induced diarrhea does not need medical attention and resolves spontaneously with either

continued use or withdrawal of the offending drug (Abraham and Sellin, 2007). Two studies found that the most commonly used and offending drugs were azithromycin, ceftriaxone, hydroxychloroquine, glucocorticoids and some antivirals (Maslennikov et al., 2021, Sultana et al., 2020). When there is more frequent diarrhea or there is the possibility of drug intolerance, adjustment of doses or cessation of the culprit drug could be the best option.

If the diarrhea in COVID-19 patients develops in the later course of illness, risk of mortality could increase and in a study, it was found that the rate of mortality due to late onset of diarrhea was 50%, compared to the lower rate (4.3%) if the onset of diarrhea was in first 20 days of the infection(Maslennikov et al., 2021). Sometimes, severe dehydration might develop and in that case hospitalization, fluid management and potassium monitoring (Desforges et al., 1990) are essential but fluid administration should be supervised continuously in the patients with severe sepsis and lungs involvement (World Health, 2020).

As there is no homogeneity in the causes of development, COVID-19 associated diarrhea requires different management for different patient. Varied combinations of antibiotics, and probiotics were used, however, none showed significant benefits over the others (Maslennikov et al., 2021). Proper use of antibiotics in case of patients with infective diarrhea required knowledge of the locally circulating pathogen spectrum and their antibiotic sensitivity pattern. Medicines like metronidazole, vancomycin, sulfasalazine, probiotic *Saccharomyces boulardii*, were also used to treat diarrhea that occurred during the later course of illness (Maslennikov et al., 2021).

Different probiotics were used for different types of diarrhea. However, the results are not always promising. Probiotics, especially *Lactobacillus* and dicotahedral montmorillonite might be another treatment option for COVID-19 associated diarrhea. Though the effectiveness of probiotics (specially *Lactobacillus* and dicotahedral montmorillonite) is still unknown for human-coronavirus associated diarrhea, it worked for animal coronavirus-associated diarrhea (V. J et al., 2010).

In critically ill patients, antibiotic-associated diarrhea or *Clostridium difficile* infection (CDI) may occur and as a treatment option or preventive measure, *Lactobacillus* containing probiotic preparation might be administered if CDI tests are found positive for COVID-19 patients (Maslennikov et al., 2021).

As the COVID-19 associated liver injury is often caused by mostly antiviral drugs like lopinavir and ribavirin, antipyretic analgesics, antibiotics and herbal products, controlled use or complete suspension of these drugs can be the only way of avoiding liver injury. Another preferable way can be a dynamic observation of the patients with elevated AST/ALT level.

5. Gaps in Knowledge

Though diarrhea is one of the most prevalent symptoms of COVID-19, not enough studies were conducted regarding this. Molecular pathophysiology is also not well established, most of them are hypothesized. Studies relate to other GIT manifestations like anorexia, nausea and vomiting are also insufficient and causes are less known. Geographical location-based studies to observe

the relationship between these symptoms and ethnicity is less published. Moreover, potential cofounder of GIT symptoms- adverse effects of drugs, gut microbiota dysbiosis, and inflammatory responses can change the prevalence of these symptoms in COVID-19 patients. More studies are needed to evaluate the degree of damage and extent of the risk due to SARS-CoV-2 infection and GIT manifestations.

6. Conclusions

Diarrhea is the most frequent gastrointestinal symptom in COVID-19 patients. ACE2 is the main receptor for entry into the gut epithelial cell which is found abundantly in the intestine. The virus enters into enterocyte and replicates there, leading to an inflammatory response in the intestine, and production of various pro-inflammatory chemokines and cytokines. Some of them trigger the increase of permeability. Viroporins of SARS-CoV-2 also directly contribute to ionic imbalance in intestine resulting in COVID-19 associated diarrhea. Another gut-specific mechanism of COVID-19 is the dysregulation of the ACE2:B0AT1 complex and the modification of this complex reduces Na+ uptake and amino acid starvation which is a contributing factor to diarrhea. Alteration of gut microbiota and side effects of medications are also involved in causing diarrhea.

As medication choice to treat the COVID-19 associated symptoms may lead to further complications like liver damage, dynamic monitoring of liver function as well as cytokine production is a must to check for further complications and fatality. Extensive studies regarding ACE2 and immune responses should be conducted in future to treat COVID-19 and ACE2 can be a good target for the COVID-19 vaccine.

Author Contributions

RTJ and SAS designed the concept of the review manuscript. RTJ prepared the first draft. SAS reviewed and edited the review with appropriate key points and figures. MS assisted in writing the management. RH made further contribution in the draft version. MSA supervised and revised the manuscript. All authors have read and agreed to this version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure 1

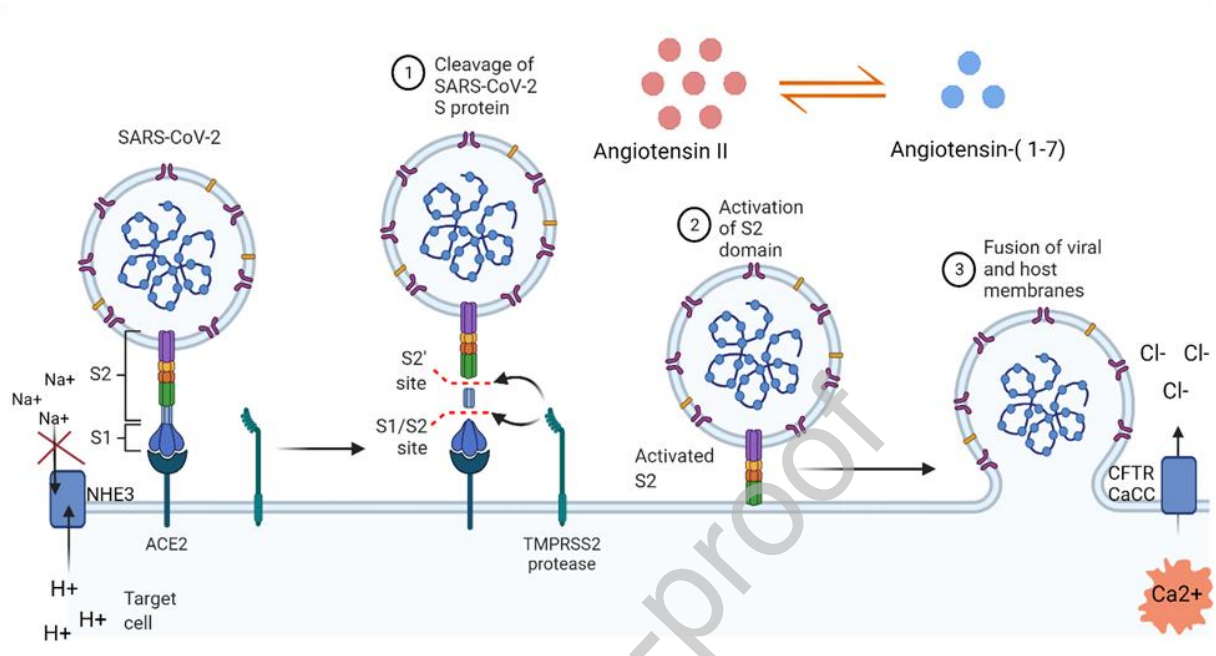

Figure 1: **Partial mechanisms of COVID-19 associated diarrhea.** SARS-CoV-2 binds to ACE2 receptor and the S protein of viral envelop is cleaved into S1 and S2 (1). Activated S2 leads to the fusion of viral membrane and host cell membrane (2 & 3). Entry of the virus into the host cell causes ionic imbalance in the host contributing to a leaky gut. ACE2: Angiotensin-converting enzyme. NHE3: Na^{+}-H^{+} exchanger 3. CaCC: Ca^{2+} activated Cl^{-} Channel. CFTR: CF Transmembrane conductance regulator. This figure was partially adapted from 'Mechanism of SARS-CoV-2 Viral Entry' by BioRender.com (2022) and retrieved from https://app.biorender.com/biorender-templates.

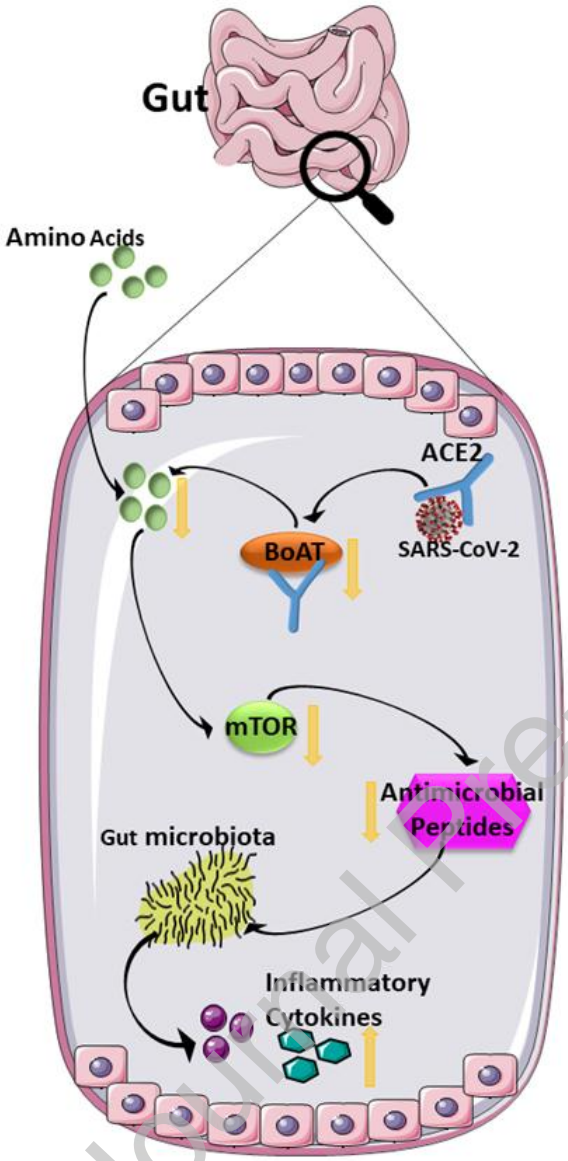

Figure 2 **: Mechanisms involved in COVID-19 associated diarrhea.** SARS-CoV-2 enters into a host cell by ACE2 receptor where it disrupts the B_0AT/ACE2 absorption pathway and then interrupts the activation of mTOR resulting in the reduction of antimicrobial peptide production. Altogether, these affect the normal gut microbiome contributing to inflammatory cytokine production. This figure was partially generated by Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.