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MINIREVIEWS

Transmembrane serine protease 2 and angiotensin-converting enzyme 2 anti-inflammatory receptors for COVID-19/inflammatory bowel diseases treatment

Naser-Aldin Lashgari, Nazanin Momeni Roudsari, Saeideh Momtaz, Amir Hossein Abdolghaffari

ORCID number: Naser-Aldin Lashgari 0000-0003-0502-6114; Nazanin Momeni Roudsari 0000-0003-1230-7969; Saeideh Momtaz 0000-0003-3957-3300; Amir Hossein Abdolghaffari 0000-0001-9961-9097.

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Naser-Aldin Lashgari, Nazanin Momeni Roudsari, Amir Hossein Abdolghaffari, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran 1941933111, Iran

Saeideh Momtaz, Amir Hossein Abdolghaffari, Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj 141554364, Iran

Saeideh Momtaz, Amir Hossein Abdolghaffari, Toxicology and Diseases Group (TDG), Pharmaceutical Sciences Research Center (PSRC), The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran 1941933111, Iran

Saeideh Momtaz, Amir Hossein Abdolghaffari, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 1941933111, Iran

Saeideh Momtaz, Amir Hossein Abdolghaffari, Gastrointestinal Pharmacology Interest Group (GPIG), Universal Scientific Education and Research Network (USERN), Tehran 1941933111, Iran

Corresponding author: Amir Hossein Abdolghaffari, PhD, Assistant Professor, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, No. 99 Yakhchal, Gholhak, Shariati St., Tehran 1941933111, Iran.
amirhosein172@hotmail.com

Abstract

Inflammatory bowel diseases (IBD) refer to a subgroup of chronic, progressive, long-term, and relapsing inflammatory disorders. IBD may spontaneously grow in the colon, and in severe cases may result in tumor lesions such as invasive carcinoma in inflamed regions of the intestine. Recent epidemiological reports indicate that old age and underlying diseases such as IBD contribute to severity and mortality in patients with coronavirus disease 2019 (COVID-19). Currently, the ongoing COVID-19 pandemic caused serious morbidity and mortality worldwide. It has also been shown that the transmembrane serine protease 2 is an essential factor for viral activation and viral engulfment. Generally, viral entry causes a 'cytokine storm' that induces excessive generation of proinflammatory cytokines/chemokines including interleukin (IL)-6, IL-2, IL-7, tumor necrosis factor-α, and interferon-γ. Future research could concentrate on developing inflammatory immunological responses that are efficient to encounter COVID-19.

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Current analysis elucidates the role of inflammation and immune responses during IBD infection with COVID-19 and provides a list of possible targets for IBD-regulated therapies in particular. Data from clinical, *in vitro*, and *in vivo* studies were collected in English from PubMed, Google Scholar, Scopus, and the Cochrane library until May 2021.

Key Words: Inflammatory bowel diseases; COVID-19; Transmembrane serine protease 2; Inflammation; Pro-inflammatory; Immunological responses

Core Tip: This article provides clinical evidence on synthetic or natural-based transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) inhibitors, which are able to reduce coronavirus disease 2019-induced inflammation and cytokine storms in inflammatory bowel disease patients. Hence, targeting TMPRSS2 and ACE2 could be noticed as a novel approach for inflammatory bowel diseases treatment.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a primarily respiratory ailment that is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), additionally named as 2019 novel COVID. It is profoundly overwhelming with case casualty rates of 2%-3%. Since its appearance in December 2019 in China, COVID-19 has quickly spread and influenced populaces in virtually all areas of the world[1,2]. Old-age patients and those with chronic conditions are more prone to dreariness and mortality in COVID-19. This high mortality is implicated in misrepresented and misled invulnerable reactions that cause cytokine storms. In brief, SARS-CoV-2 infects the angiotensin-converting enzyme 2 (ACE2) expressing epithelial cells in the lung and/or the intestine, leading to a massive production of mediators that induce the immune cell activation. Overactivation of immune cells leads to severe complications including acute respiratory distress syndrome, shock, and multiorgan failure[3,4].

Inflammatory bowel diseases (IBD) include two major types: Ulcerative colitis and Crohn's disease. IBD is characterized with persistent resistant interceded sicknesses that regularly require immunomodulatory and immunosuppressive treatments[5,6]. Therefore, patients with IBD are at high risk to different shrewd viral and bacterial contaminations. There is no solid evidence that patients with IBD are at higher risk for COVID-19 infection, although it has been indicated that patients with IBD who are pregnant are more vulnerable[7]. The current study discusses the impact of COVID-19 on IBD[8,9]. We provide evidence on mediatory effects of the transmembrane serine protease 2 (TMPRSS2) and ACE2 signaling pathways against inflammation and introduces the synthetic or natural TMPRSS2 and ACE2 inhibitors as probable approaches for IBD treatment in the COVID-19 situation[9,10].

LITERATURE SEARCH

PubMed, Google Scholar, Scopus, and Cochrane Library were searched and relevant clinical, *in vivo*, and *in vitro* articles (in English) were collected until May 2021. Search terms included "corona virus" OR "COVID-19" AND "inflammatory bowel disease" OR "IBD" OR "inflammation" AND "TMPRSS2" OR "ACE2" AND "TMPRSS2 inhibitors"

OR "ACE2 inhibitors".

COVID-19 PATHOGENESIS

Variations in potency of the SARS-CoV-2 cell entry may account for discovering new solutions to deal with the virus. It has been reported that the entrance of SARS-CoV-2 to the human cells victimizes the SARS-CoV receptor ACE2 and TMPRSS2 for the spike (S) supermolecule priming. It is debatable whether the metallopeptidase domain seventeen [a disintegrin and metalloprotease domain 17 (ADAM17), also referred to as the tumor necrosis factor (TNF)-α-converting accelerator] located in the ACE2 ectodomain shedding may or may not counteract the virus entry by increasing the number of soluble ACE2, or it solely contributes to the ACE1/ACE2 unbalancing, inflammation, and occlusion[11]. The ACE2-receptor/S-protein interaction could be a key factor for success of virus infection and willingness. Similarly, single ester polymorphisms located inside the TMPRSS2 factor (21q22.3) can play a more important role in respiratory disorder[12]. ACE1 and ACE2 collaborate with the renin-angiotensin system to balance the native vasoconstrictor/proliferative ACE1/angiotensin II/angiotensin II type 1/angiotensin (Ang) II/Ang type 1 receptor (ACE1/Ang-II type 1/AT1-axis), and vasodilator/antiproliferative (ACE2/Ang1-7/mitochondrial assembly-axis) actions. This ends up in the protection of organs and blood vessels by the decoagulants, medicinal drugs, anti-proliferation, anti-fibrosis, anti-alveolar vegetative cell caspase-mediated cell death, and anti-oxidative stress activities that are able to antagonize the Ang-II effects[11,13].

TMPRSS2 AND ACE2 STRUCTURE AND RELATED SIGNALING PATHWAYS

In a complex pathophysiological condition like COVID-19, the ACE2 cytoplasmic tail cleavage intervened by TMPRSS2 is a significant event to be considered (Figure 1). Cleavage of the ACE2 tail by TMPRSS2 increases viral load in objective cells, and TMPRSS2 could facilitate the SARS-CoV-2 passage *via* the SARS-S cleavage, which induces the S protein for film combination. The ACE2 cleavage may enhance viral uptake through the cathepsin L-subordinate pathway, resulting in viral integration with the endosomal layer and eventually cell contamination[11,14]. In spite of similar explicitness of TMPRSS2 and ADAM17 for ACE2, they act opposite for cleavage of ACE2. To start with, the divisions produced by the cleavage of these proteases have distinctive subatomic sizes, mainly due to various cleavage locales. Second, cleavage of ACE2 by ADAM17 forms the ACE2 ectodomain, which is shed into the extracellular medium, as the soluble ACE biologically dynamic structure[15,16]. *In vitro* studies have shown that the ACE2 ectodomain does not separate from the TMPRRS2-induced ACE2 cleavage. This was evidenced by a C-terminal intracellular cleavage. In this manner, the distinctions in the cleavage destinations and its organic outcomes might be basic. For sure, just the soluble ACE2 structure would have a defensive impact on prevention of viral particle aggregations[17]. Therefore, overexpression of ADAM17 and TMPRSS2 could be a primary factor in inflammation storm that is characterized by negative features such as renin-angiotensin system lopsidedness, intense irritation, and intravascular coagulation in older populations with COVID-19 comorbidities. Initiation of inflammation cycles is a key element for SARS-CoV-2 contamination[18,19].

TMRPSS2 AND ACE2 INFLAMMATORY PATHWAY

ACE2 is the main receptor for SARS-CoV-2, providing additional insurance against the destructive impacts of viral diseases. Moreover, as referenced above, solid confirmations indicate that the outflow of ACE2 is dependent on the companion of hormonal, hereditary, and age-related systems[20,21]. Overaction of ADAM17 in both COVID-19 and the plasma level of ACE2 has been confirmed by several reports. Overexpression of the *ADAM17* gene and its protein level have been implicated in several inflammatory conditions including IBD[22,23]. High levels of inflammatory cytokines and chemokines in COVID-19 patients are accounted for by more elevated levels of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon

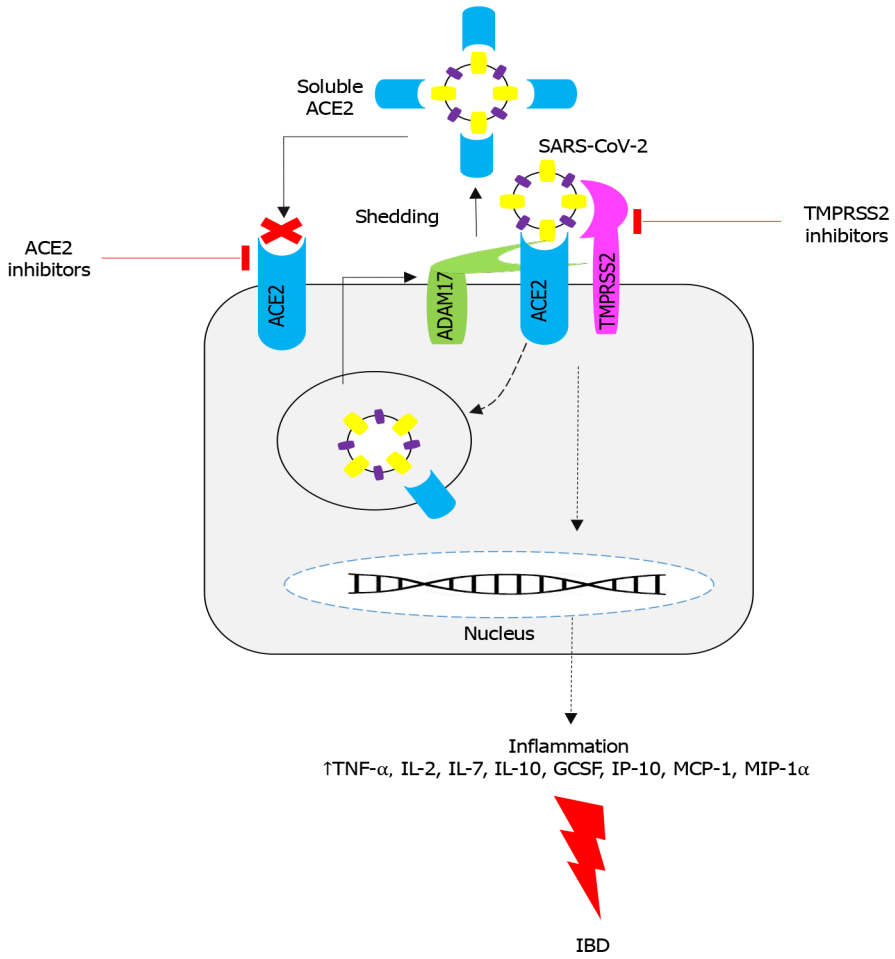

Figure 1 Coronavirus disease 2019 induced inflammatory bowel diseases mechanism. ADAM17: A disintegrin and metalloprotease domain 17; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2; GCSF: Granulocyte colony-stimulating factor; IP-10: Interferon gamma-induced protein 10; MCP1: Monocyte chemoattractant protein 1; MIP1-α: Macrophage inflammatory proteins-α; IBD: Inflammatory bowel diseases.

gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory proteins-1A, and TNF-α. A significant effect of the "fiery wave" in COVID-19 indicates the cytokine storm may be firmly connected with the seriousness of the infection[24,25]. The 'cytokine storm' is a significant target for research about the pathogenic cycles in SARS-CoV–2 contaminations and is a way to recognize new restorative targets. On the other hand, blockade of SARS-CoV–ACE2 in the ACE2 cytoplasmic domain pathway results in upregulation of ADAM17 activity. Upregulated ADAM17 increases the ACE2 ectodomain proteolytic cleavage[26,27]. Similar to the ACE2 tail cleavage, ADAM17 upregulation is essential for SARS-CoV infection. Finally, excessive activity of ADAM17 induces proinflammatory mediators, thus upregulating the inflammatory pathway during SARS-CoV-2 infection. ACE2 can be cleaved by the activity of TMPRSS2 protease[28,29]. TMPRSS2-induced ACE2 cytoplasmic tail cleavage may incite the viral uptake through a cathepsin L-subordinate pathway. Of note, acute respiratory distress syndrome is a delayed consequence of an aberrant generation of proinflammatory cytokines/chemokines or the 'cytokine storm' by effector cells[30-32].

COVID-19 INDUCED IBD: CORRELATIONS AND OVERLAPPING OF INFLAMMATORY PATHOGENESIS

The SARS-CoV-2 receptor ACE2 and TMPRSS2 receptor are central factors in COVID-19-induced IBD pathogenesis (Table 1 and Figure 1). These receptors are often found within the lower respiratory lot of pneumocytes and the gastrointestinal tract[7]. The ACE2 receptors are frequently located within the terminal ileum and colon. It was

Table 1 Clinical evidences of coronavirus disease 2019-induced inflammatory bowel diseases treatment

Ref.	Clinical studies	Model of IBD	Intervention	Duration of treatment	Numbers of animals in intervention group and control group	Outcomes	Adverse effects
Nowak *et al*[25]	Clinical trial	IBD in COVID-19	-	-	138 treatment naïve IBD patients (cases) and 154 controls	↑ACE2/TMPRSS2 expression; ↑ Inflammation	-
Brenner *et al*[67]	18 yr (with IBD), the Pediatric IBD Porto Group	-	TNF antagonist monotherapy (48%), followed by sulfasalazine/mesalamine (23%)	March 2020-October 2020	Hospitalized cases (n = 14); Outpatient cases (n = 195)	Sulfasalazine/Mesalamine and steroid therapy were associated with increased hospitalization risk and TNF antagonist monotherapy was associated with decreased risk parallel those reported in adult IBD patients. PIBD patients have a relatively low risk of severe COVID-19, even when receiving biologic and/or other immune-suppressive therapies for their IBD	-
Norsa *et al*[85]	Clinical trial	Crohn disease and Ulcer colitis	Anti-inflammatory (Salicylates); thiopurines or methotrexate; biologics (Infliximab, Adalimumab, Ustekinumab, Vedolizumab, Golimumab); steroids; Other immunosuppressants (Tacrolimus, Cyclosporin, Mofetil Micofenolate)	February 2020-March 2020	Crohn disease = 186; Ulcer colitis = 336	IBD improvement: ↓TNF-α; ↓ Inflammation; ↓ACE2/TMPRSS2 expression	-
Mazza *et al*[86]	Clinical trial	Ulcerative colitis	Methylprednisolone (40 mg/d); prednisone dosage at the time of patient's death was 25 mg daily	December 2019-February 2020	-	IBD improvement; Improvement in COVID-19 symptoms; ↓ Inflammation	-
Tursi *et al* [87]	Clinical trial	Crohn's disease	Adalimumab	-	-	Maintain of IBD remission during COVID-19; Managing/preventing COVID-driven pneumonia: ↓TNF-α ; ↓Inflammation; ↓ACE2/TMPRSS2 expression	-
Bodini *et al*[88]	Clinical trial	IBD	Immunosuppressants/biological treatment	3 wk	48 patients	IBD improvement; Improvement in; COVID-19 symptoms	Increase the risk of infection
Tursi *et al* [89]	Clinical trial	Crohn's disease	Mesalazine (3 g/d) and Adalimumab 40 mg subcutaneously	-	74 cases	IBD improvement; Improvement in COVID-19 symptoms; ↓TNF-α; ↓ Inflammation; ↓ACE2/TMPRSS2 expression	-
Allocca *et al*[90]	Clinical trial	IBD	Biological treatment	-	162 IBD patients	IBD improvement; Improvement in COVID-19 symptoms	-
Jacobs *et al*[91]	Clinical trial	Ulcerative colitis	Tofacitinib (10 mg twice daily)	5 mo	-	IBD improvement; Improvement in COVID-19 symptoms	Increase the risk of infection
Gutin *et al*[69]	Clinical trial	Ulcerative colitis	Biological treatment	February 2020-March 2020	522 patients	IBD improvement; Improvement in COVID-19 symptoms: ↓TNF-α; ↓ Inflammation; ↓ACE2/TMPRSS2 expression	
Taxonera *et al*[92]	Clinical trial	Crohn's disease	Immunomodulatory/biologics	-	n = 12	IBD improvement; Improvement in COVID-19 symptoms; ↓TNF-α; ↓ Inflammation; ↓ACE2/TMPRSS2 expression	
Allocca *et al*[93]	Clinical trial	-	Immunosuppressant or biologics	-	n = 15	IBD improvement; Improvement in COVID-19 symptoms; ↓TNF-α; ↓ Inflammation	-
Mak *et al* [94]	Clinical trial	IBD in COVID-19	Thirty (75%) were on 5-Aminosalicylates acid, 15 (37.5%) on	-	n = 63	IBD improvement; Improvement in COVID-19 symptoms; ↓	-

			immunosuppressants (14 Thiopurine, one Tacrolimus), 11 (27.5%) on corticosteroids and 7 (17.5%) on biologics (3 Infliximab, 1 Adalimumab, 2 Vedolizumab and 1 Ustekinumab)			Inflammation	
Bardasi and Alvisi [95]	Clinical trial	Crohn's disease in COVID-19	Subcutaneous administration of 40 mg Adalimumab	6 mo	-	IBD improvement; Improvement in COVID-19 symptoms ↓ Inflammation	-
Ashton *et al*[96]	Clinical trial	IBD in COVID-19	Anti-TNF therapy (Infliximab or Adalimumab)	-	*n* = 122	IBD improvement; Improvement in COVID-19 symptoms: ↓TNF-α; ↓ Inflammation	-

ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; IBD: Inflammatory bowel diseases; TNF: Tumor necrosis factor.

shown that the convergence of these receptors was higher in IBD patients, in both the energetic and calm stages of the disease[33]. The ACE2 receptors are a part of the renin angiotensin-aldosterone system that is assumed to play critical roles in controlling the provocative handle. Terminal ileum and the colon are the most affected areas in IBD [34]. IBD is also correlated with upregulation of inflammatory cytokines and the ACE2 receptors. As we discuss in this article, patients with IBD do not seem powerless against COVID-19[35]. In this context, a few theories have been proposed. For instance, the renin angiotensin-aldosterone system has two specific pathways involved in irritation course. Multiple studies confirmed that ACE2 is upregulated in IBD, and in the SARS-CoV-2 condition ACE2 exacerbates the disease symptoms. Accordingly, prevention of the ACE2 protein expression has been suggested for controlling both COVID-19 and IBD[36,37]. While the ACE-angiotensin receptor 1 pathway is favorable for inflammation, the ACE2 pathway helps in tissue security. Given the enteric inflammation in IBD, it has been suggested that the ACE2 receptors and the host cell surface proteases like TMPRSS2 may suppress SARS-CoV-2[38,39]. The ACE2 level was shown to be downregulated in colonic aggravation in animal models; thereby, some IBD drugs such as steroids and biologics were found useful for cutting down the ACE2 in infected cells. Another report declared no change in ACE2 receptors or TMPRSS2 in IBD patients when diverged from controls[40,41].

IBD IN COVID-19: TREATMENT APPROACH

As mentioned, there are limited data on the possible impact of SARS-CoV-2 contamination on patients with IBD. Various methodologies can be utilized alone or concurrently to conquer the infection. Blockage of the ACE2 receptors and the viral S protein are the main focus of current investigations on SARS-CoV-2 regulation. So far, we discussed that blockage of the TMPRSS2 receptor and/or the ACE2/TMPRSS2 complex is likewise a plausible approach to modulate this infection. In this context, a number of synthetic or natural TMPRSS2 and ACE2 inhibitors that are able to mediate the TMPRSS2 and ACE2 signaling have been explored.

Natural agents targeting TMRPSS2 and ACE2 to manage the COVID-19 and IBD overlap

Medicinal plants are the greatest age-old wellspring of remedially valuable phytochemicals that are utilized to keep up human's wellbeing and to forestall and treat numerous infections. Medicinal plants and spices are used in Ayurveda, a conventional and optional restorative treatment in light of comprehensive body recuperating, which began in the Indian subcontinent[42,43]. Enormous investigations are right now centered on understanding the remedial viability and the activity of these phytochemicals. An improved dietary regimen along with natural medicinal formulations may provide preventive strategies for intense respiratory diseases, aspiratory fibrosis, pneumonia, sepsis, and numerous organ failure, which are hallmarks of serious COVID-19 contamination[44]. Also, a significant number of these phytochemicals help the insusceptible framework and instills insurance against infective diseases. It was shown that oxidative stress and many other reasons, notwithstanding existing comorbidities, add to a large number of difficulties related to coronavirus disease. Herein, we introduce plant species that contain various phyt-

ochemicals with antiviral, antifibrotic, cell reinforcement, mitigating, and immunomodulatory properties[45]. These phytochemicals, when used in blend, could have synergistic impacts, either as prophylactic or as steady specialists to limit certain clinical manifestations observed in COVID-19-contaminated patients. Moreover, certain types of microscopic organisms, green growth, and parasites may have remedial impacts against pneumonic fibrosis and intense lung injury[46].

ACE2 is found in the outer layer of the human cell that is accounted as a likely coupling site for the S protein. A couple of experiments have shown that there is a strong link between ACE2 and the S protein. Thus, blockade of ACE2 by phytochemicals is a strategy to fight SARS-CoV-2[47]. Several studies reported that SARS-CoV-2 is able to infect the central nervous system through TMRPSS2 and ACE2 receptors. It was also shown that ACE2 participates in neuroprotective responses, hence playing a critical role in treatment of COVID-19. Phytochemicals such as baicalin, scutellarin, and hesperetin can bind to ACE2 and prevent neurological impairments caused by COVID-19.

It was shown that hesperidin, chrysin, and emodin are also effective for COVID-19 treatment by attenuating the harmful effect of viral infection within cells[48]. Kaempferol, quercetin, and fisetin can bind with human angiotensin-converting enzyme-S-protein. In silico studies demonstrated that quercetin, quercetin 3 glucuronide-7-glucoside, quercetin 3-vicianoside, absinthin, glabridin, and gallic acid have strong affinity toward ACE2 to suppress COVID-19. Nuclear docking examination elucidated that dithymoquinone (aquinone) encounters the COVID-19 neurological side effects through blockade of ACE2. An in silico study reported that two chalcones namely azobechalcone and isolophirachalcone and some alkaloids (*i.e.* fangchinoline and tetrandrine) had high limiting proclivity to the S protein of SARS-CoV-2[49]. Flavonoids reduce the ACE2 expression through inducing the nuclear factor erythroid 2-related factor 2, thus fighting SARS-CoV-2 by means of their antioxidant properties. Kaempferol, quercetin, and fisetin are promising flavonoids against COVID-19-induced adverse neurological effects. Stilbenes, in particular resveratrol, are promising candidates for COVID-19 treatments, mainly by disturbing the formation of the S protein and the ACE2 receptor complex[50]. A variety of phenolic compounds including naringenin, hesperetin, hesperidin, and baicalin (alone or in combination) showed inhibitory effects on ACE2 activity and can be considered as potential treatments for COVID-19[51].

Different studies exhibited that some other phenolic compounds such as cinnamaldehyde as well as terpenoids such as carvacrol, geraniol, anethole, L-4-terpineol, cinnamyl acidic, thymol, and pulegone possess antiviral activities through blockade of the viral S protein[52,53]. It was reported that the binding affinity of ACE2 linkage with scutellarin (a flavonoid glycoside) and glycyrrhizin (a triterpenoid) was stronger than baicalin, hesperetin, and nicotianamine[54].

Limonoids and triterpenoids also displayed similar inhibitory effects on ACE2. Another in silico study similarly demonstrated that limonin, obacunone, ursolic destructive, glycyrrhizin destructive, 7-deacetyl-7-benzoylgedunin, maslinic acid, and corosolic acid effectively target SARS-CoV-2 proteins[55]. In this line, nimbin (a triterpenoid) and curcumin exhibited high limiting proclivity on ACE2 and the S protein [56]. Epigallocatechin-3-gallate and theaflavin gallate were shown to have inhibitory effects on the S-protein central channel of SARS-CoV-2. Moreover, three alkaloids, including cepharanthine, fangchinoline, and tetrandrine, inhibited the S protein of Human coronavirus Subtype OC43 (Human-CoV-OC43) expression, while tetrandrine exhibited moderating effects on viral sicknesses. An indazole alkaloid isolated from the seeds of *Nigella sativa*, called nigellidine, was shown to bind the dynamic areas of SARS-CoV-2, thereby paralyzing the virus. In another study, anthraquinone emodin blocked the ACE2 and S protein conjunction[57,58].

Chemical agents targeting TMRPSS2 and ACE2 to manage the treatment of COVID-19 and IBD overlap

Various classes of medications, with different powers and immunosuppressive potentials, are used for IBD treatment (Table 1 and Figure 1). At present, limited data are available for the utilization of different medications in IBD under the COVID-19 condition, henceforth the level of proof is not yet certain[59]. Current suggestions, proposed by specialists and different social orders, are overwhelmingly based on the recounted proof from the utilization of these medications during other viral pandemics like SARS and Middle East respiratory syndrome coronavirus or a few distributed case reports[60]. By and large, usage of intense immunosuppressants in IBD patients should be limited, except if totally essential. Notwithstanding, patients

who are on stable upkeep portions may keep on doing as such with close contact with their physicians[61,62].

Salicylates: Salicylates are usually utilized in either oral form or as a bowel purge. They have a neighborhood activity and are improbable to influence the course of COVID-19 when are used in IBD patients, thereby they may be securely proceeded in dosages[63].

Corticosteroids: Corticosteroids are the most common drugs that are used in IBD, mainly due to their intense calming effects. Therefore, steroids may be valuable in suppression of COVID-19, particularly in conditions like intense lung injury, intense respiratory trouble disorder, and septic shock. During the SARS and Middle East respiratory syndrome pandemic, corticosteroids treatment helped to postpone viremia [64,65], while there were no general improvement in terms of septic shock or psychosis, *etc.*[66]. Given the absence of adequacy, the World Health Organization suggested that routine corticosteroids ought to be avoided except in explicit circumstances. Steroids are possibly kept away from the first line therapies in recently analyzed IBD patients. Notwithstanding, considering their tremendous advantages in IBD, it was suggested that the main steroids might be beneficial at low doses in patients with COVID-19 and IBD, specifically in patients that are already on treatment [67,68]. Steroids with limited site of action, for example budesonide, seem harmless to be used. Infliximab might be a therapeutic option for COVID-19 positive patients with mild respiratory symptoms[61,69].

Cyclosporin: Cyclosporin is used for serious ulcerative colitis as an option in contrast to steroids. Although, some data pointed out that cyclosporine can inhibit the coronavirus replication proteins *in vitro*, its prescription is controversial in patients with COVID-19 due to its strong immunosuppressive properties[70-72].

Azathioprine and methotrexate: Azathioprine is a thiopurine that is often used for IBD treatment, particularly for upkeep treatment. Curiously, past investigations have demonstrated that thiopurine analogs have both immediate and roundabout activities on smothering antiviral movement. They also hinder viral proteases once the host proteins were engaged with viral replication[73,74]. Depending on the perception of genuine viral contaminations in IBD patients who are using thiopurine, the treatment time can be estimated. Interruption in treatment up to 14 d after recuperation from COVID-19 has been suggested. Methotrexate can perhaps continue without issues[75, 76].

Biologics: Current data show that infliximab and adalimumab (TNF-α inhibitors) have no unfavorable effects on the clinical course of COVID-19[62,77]. One reason speculated is the strong mitigating impact of TNF blockage, which may indeed constrict the cytokine storm in serious types of COVID-19[78,79]. Co-administration of medicines (*i.e.* thiopurine and infliximab) might be an option. Also, monotherapy with natural products may be considered[60,80,81]. Vedolizumab (an adversary of α4β7 integrin) is significantly explicit for movement on the gut, hence it is favorable for fundamental or pneumonic responses in COVID-19[62,82]. Ustekinumab is an approved clinical therapy for patients with IBD. Ustekinumab is a cytokine antibody and an inhibitor of IL-12 and IL-23. Currently, there are no major concerns about usage of ustekinumab in patients with IBD and COVID-19. Vedolizumab or ustekinumab might be the primary therapeutic options for individuals at higher risk of COVID-19 if biological treatments are thought of[79,83,84].

CONCLUSION

Information on the physiologic and pathophysiologic functions of ACE2/TMPRSS2 is still scant. ACE2/TMPRSS2 is very much described in the cardiovascular and renal frameworks. Yet little data exist regarding other organ frameworks, for example the gastrointestinal system. Moreover, specific function of the ACE2/TMPRSS2 axis in pathologic conditions was traditionally restricted to cardiovascular illnesses. Although, considering the ACE2/TMPRSS2 as a multifunctional protein has accomplished significance as of late.

The current COVID-19 pandemic has featured the importance of ACE2/TMPRSS2 as a receptor for SARS-CoV-2, yet research is expected to determine whether the ACE2/TMPRSS2 levels enhance the pathogenesis of COVID-19 or could benefit the course of illness by diminishing the malicious impacts of Ang II. Moreover, the

relationship between ACE2/TMPRSS2, the intestinal amino corrosive vehicle, and IBD merits further consideration in patients with IBD. At last, association of ACE2/TMPRSS2 to integrins raises concerns and expectations, particularly because there were just two articles regarding the matter. Taking everything into account, investigating the multifunctional nature of ACE2/TMPRSS2 in IBD (by describing its appearance/movement in the blood, gut, as well as excrement of patients with IBD and solid control patients) will develop the knowledge on the pathophysiology of this illness. In accordance with this objective, recognizable proof of other biomarkers of infection movement, treatment reaction, and new medication target, as well as setting of the novel helpful alternatives is required to affect tolerant consideration.

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