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Updated information on new coronavirus disease 2019 occurrence, drugs, and prediction of a potential receptor

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Abstract

The new coronavirus (COVID-19) was first reported in Wuhan in China, on 31 December 2019. COVID-19 is a new virus from the family of coronaviruses that can cause symptoms ranging from a simple cold to pneumonia. The virus is thought to bind to the angiotensin-converting enzyme 2, as a well-known mechanism to enter the cell. It then transfers its DNA to the host in which the virus replicates the DNA. The viral infection leads to severe lack of oxygen, lung oxidative stress because of reactive oxygen species generation, and overactivation of the immune system by activating immune mediators. The purpose of this review is to elaborate on the more precise mechanism(s) to manage the treatment of the disease. Regarding the mechanisms of the virus action, the suggested pharmacological and nutritional regimens have been described.

KEYWORDS

ACE2, COVID-19, immune mediators, inhibitory mechanisms, pneumonia

1 | INTRODUCTION

Coronaviruses are a large family of pathogens.[1] Several members of this superfamily cause mild illnesses[2-4]; however, some viruses impart fatal infections.[5] The virus was named coronavirus because of the crown-shaped appearance which is characterized by spikes similar to a crown. Several coronaviruses infect animals[6] some of which evolved in their animal hosts that can infect humans. The first type of human infection was recognized in the 1960s[7] but since then, seven human-infecting coronaviruses have been registered, including the 2019-nCoV, also recognized as Wuhan Coronavirus.[8]

Coronaviruses are divided into four supergroups; namely alpha, beta, gamma, and delta coronavirus.[9] In the context of pathogenicity, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) were identified earlier.[9] As mentioned, the hosts of coronaviruses are both humans and animals, including poultry and mammals. Coronavirus disease (COVID-19) belongs to a superfamily of viruses that are transmitted between animals and man in a phenomenon called zoonosis,[1,10] and can commonly cause severe acute respiratory syndrome (SARS), pneumonia, renal failure, and reproductive toxicity, and even death.[11,12] According to the Center for Disease Control and Prevention (CDCP), SARS and MERS started with bat infections and then mutated to infect humans.[13]

1.1 | The outbreak of COVID-19 in Iran and the world

Until 23 June 2020, there were more than 9 192 700 confirmed cases of COVID-19 in the world, with 474 445 deaths and 4 939 422 individuals recovering from the infection. The first report of the confirmation of the virus came from Wuhan, China, on 31 December 2019.[14,15] Since then, COVID-19 has been identified in many more countries. The greatest incidence of the disease has been recorded in the USA, Brazil, Russia, India, UK, Spain, Peru, Chile, and Iran.

There are contradictory reports regarding the published statistics from Iran, with several international media reporting a much higher incidence of infection and death due to the coronavirus. The World Health Organization (WHO) has issued a worldwide warning[16] as the number of infected individuals has been increasing daily due to the simple route of transmission to humans, including face-to-face contact and direct contact with infected persons.[8]

2 | HISTORY OF THE CORONAVIRUS

In 1960, coronavirus was first recognized as the cause of the common cold.[13] In a study conducted in 2001 in Canada, more than 500 patients developed flu-like symptoms, and virological analysis, using polymerase chain reaction, revealed that 3.6% of the cases were HCoV-NL63 strain positive.[13] Before 2002, coronavirus was known as a comparatively simple nonlethal virus.[13] However, the outbreak in Guangdong province, China, from 2002 to 2003 caused severe SARS which was spread to many countries, including Taiwan, Thailand, Hong Kong, Vietnam, the United States, and Singapore.[17] A total of 8096 people were infected with the virus, causing 774 deaths. There were 50 SARS patients in Hong Kong, of whom, more than 60% were positive for coronavirus.[18] In 2004, the WHO and CDCP declared an emergency state.[16,19] Meanwhile, there is ample evidence demonstrating that coronaviruses were not stable and could transform into viruses that are more toxic and even lethal to humans.[13] An outbreak of MERS coronavirus, resulting in many deaths, was first reported in Saudi Arabia 2012.[20] The virus spread first to other Middle Eastern countries, and then to other parts of the world, thus generating new interests in the study of COVID-19.

3 | SYMPTOMS

The symptoms of COVID-19 appear within a few hours or up to several days after the entry of the virus to the human body and depend on the health conditions of the patient such as the underlying diseases. The symptoms of the Wuhan virus disease are generally similar to other respiratory infections. Infected individuals could develop fever, cough, and shortness of breath, similar to the SARS-CoV symptoms, and some patients have vomiting, diarrhea, and related stomach symptoms.[13] The worst cases manifest with pneumonia, SARS, renal failure, and death. According to the CDCP, some infected patients have little or no symptoms, while others may be seriously ill or die of the disease in an age-dependent manner. Preliminary estimates indicated that symptoms could persist for 2 to 14 days.[13]

4 | TRANSMITTANCE

Health experts generally believe that some human infections were associated with the large live animal/seafood markets in Wuhan, suggesting that the disease was first transmitted from animals to humans. Human-to-human transfers were quickly confirmed in China, Iran, the United States, and Germany.[13] The first infected individual in the United States was a man in Illinois in his 60s whose wife had been infected while traveling in Wuhan, China.[21] However, Iranian officials reported the first COVID-19 confirmed cases on 19 February 2020 in the holy city of Qom.[22]

5 | MUTATION

A previously-reported mutation caused the SARS outbreak from 2002 to 2003. In that mutation, a naturally-mutated virus from the civet cat was transmitted to humans. In 2012, in Saudi Arabia, a camelid coronavirus mutated to become a human infectious disease, leading to the outbreak of MERS. The origin of the Wuhan coronavirus is not precisely known but it is suspected that the virus might have originated from some wild animals that had been killed and sold for food.[13] Coronavirus-2019 contains six protein amino acids that are crucial for binding to angiotensin-converting enzyme 2 (ACE2) receptors and for determining hosting the virus. COVID-19 in five nucleotide regions of the spike proteins is similar to that reported in SARS-CoV and differs in only five residues. Genomic characteristics of COVID-19 indicated that the spike protein of SARS-CoV-2 has a functional group of furin at the S1-S2 boundary, containing 12 nucleotides surrounded by three O-linked glycans.[23] Hence, these changes in the 2019 Coronavirus may cause a greater affinity for the ACE2 receptor than other coronavirus types, including the SARS and MERS. As genetics and lifestyle may play a role in the receptor affinity,[24] the type of ACE2 receptor in countries with a high prevalence of COVID-19, including the United States, Spain, Italy, France, Germany, and the United Kingdom, may be associated with Asian countries with a lower prevalence of COVID-19.

6 | RISK FACTORS

According to WHO, several factors increase the risk of contracting the COVID-19, including high blood pressure, heart problems, and/or diabetes.[25] Older men are more susceptible, but this may also involve other contributing factors that need closer scrutiny.[26] Other contributing risk factors are stress, malnutrition, lack of sleep, chemicals, and other toxic environmental xenobiotics (such as heavy

metals, including fluoride and arsenic) that adversely impact the immune system function.[27,28] It has also been reported that some drugs and foods can modify the activity or expression of the ACE2 enzyme, and thus may increase the susceptibility to viral infections.[29-31] In accordance with the flowchart of the diagnosis and treatment of COVID-19 at the outpatient and inpatient levels of the Deputy of Public Health of the Islamic Republic of Iran, other individuals at greater risk of developing COVID-19 were immunocompromised patients; including those undergoing corticosteroid-therapy (more than 12.5 mg/d prednisolone over 2 weeks), chemotherapy, malignancies, and organ transplants, and individuals with human immunodeficiency virus (HIV), respiratory diseases, and body mass index > 40.

7 | CLINICAL FEATURES

The COVID-19 virus is much smaller than the influenza virus and can easily enter deep into the lungs, attach to more receptors, and cause severe acute respiratory complications.[32] Clinical manifestations of MERS-CoV include flu-like symptoms, such as fever and cough, chills, myalgia, rhinorrhea, and fatigue in 87% of patients, and more severe symptoms, comprising of breath shortness and respiratory failure in 48% of patients leading to the need for ventilation and intubation.[13] Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain have also been reported in approximately 35% of the cases; severe kidney failure requiring hemodialysis has been observed.[13] Physical examination also revealed that patients often experience fever and lung symptoms. Laboratory tests may reveal thrombocytopenia, lymphopenia, disseminated intravascular coagulation, and multiple organ failure, which may lead to death.[33] The human testis is also one of the targets for SARS-CoV-2 infection which might have a considerable effect on the pathophysiology of the disease. It has been shown that ACE2 was significantly enriched in the germ cells, interstitial (Leydig), and Sertoli cells.[13]

According to Huang et al, 31% of patients with COVID-19 had a fever, of which 78% had temperatures above 38°C. They also reported that 76% had a cough, 44% showed fatigue and muscle aches, and 55% dyspnea. A small number of patients also had sputum expectoration (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). Laboratory tests showed that 25% of the infected patients had leukopenia and 63% had lymphocytopenia. Aspartate aminotransferase was elevated in 37% of patients. Myocarditis was diagnosed in 12% of patients. Computerized tomography (CT) scanning of the chest is an accurate method to distinguish 100% abnormality in patients. In 98% of the infected patients, grinding glass-like and consolidation areas were found.[8] Guan et al, reporting on 1099 cases of modern coronavirus infection, found that fever (87.9%) and cough (67.7%) were the most common symptoms, with diarrhea (3.7%) and vomiting (5%) being rare. The chest CT scans were abnormal, showing grinding glass-like and consolidation areas in 96% of patients, while 82.1% of the patients had lymphopenia.[34]

8 | MECHANISM OF INFECTION

Coronaviruses cause mild respiratory infections via tissue fibrosis, cytocidal, and immune-mediated mechanisms.[35] Xia et al reported that the affinity of the COVID-19 virus to human ACE2 was highly similar to SARS-CoV.[36] ACE2 serves as the entry point into the cells for some coronaviruses.[37,38] The ACE2 enzyme is a type I membrane protein in the lungs, arteries, heart, kidneys, and intestine,[39,40] and lowers blood pressure by catalyzing the cleavage of angiotensin II (a vasoconstrictor peptide) to angiotensin 1-7 (a vasodilator).[41]

Studies on ACE2 distribution and enzymatic activity in rodents and human tissues confirmed a critical role for the renin-angiotensin system in the pathogenesis of acute lung injury in SARS-CoV.[42] ACE2 might also have a role in COVID-19 acute lung injury which is an important symptom of COVID-19. Furthermore, other symptoms of COVID-19 may also occur via this vital receptor. Clinical trials reported that most cases of COVID-19 infections were found in older male patients,[8] with no symptoms in newborns[15]; this is in accordance with the reports showing that ACE2 expression increased with age.[43] Another line of evidence indicating a role for ACE2 in COVID-19 is the higher risk in individuals suffering from diabetes, hypertension, and cardiovascular diseases where a role for ACE2 is very clear.[44,45] Taken together, the virus needs to bind with the ACE2 receptor for joining and replicating in human cells. Hence, inhibition of overexpression or activity of ACE2 might be an approach in preventing the cellular invasion of the virus.

9 | MANAGEMENT AND ANTIVIRAL THERAPY

The key treatment strategies for a typical coronavirus infection are supportive therapies, antipyretics, and painkillers (except nonsteroidal anti-inflammatory drugs [NSAIDs]), hydration maintenance, respiratory support through mechanical ventilation or extracorporeal membrane oxygenation, and in the case of bacterial super-infection, under antibiotic treatment. However, such treatments might not be adequate for protection against more severe MERS-CoV infections.[46-48]

Interferon (IFN) alpha and ribavirin can work synergistically and are more advantageous at the early stages of the disease. Mycophenolic acid was reported to be effective as a monotherapy; however, the preliminary clinical trials included a small number of patients; therefore, more investigations are needed.[49,50] Although several companies are trying to develop the COVID-19 vaccine, none is currently available; however, some American and Chinese companies have only claimed to have the COVID-19 vaccine, without any proven results.

To date, no effective anti-COVID-19 drug has been identified in clinical studies.[51] Since the outbreak of COVID-19, lopinavir-ritonavir, arbidol, oseltamivir, and IFN have been used in clinical trials[52,53] but conclusive data are yet to be confirmed.

IFN has almost no effect on a range of respiratory viral infections, the first drugs being directed against HIV and influenza infections. Remdesivir was effective in a small number of adults, but evidence-based clinical proof for children is still lacking.[54] Most children with respiratory viral infections have only mild symptoms and recover by themselves; this might be due to their rebutting immunity via their active and large thymus; hence, medical-related agencies believe that antiviral drugs should not be employed routinely except in emergencies. The objective of treatment should be to reduce symptoms and maintain immune balance.[55] An effective method of drug discovery is to examine whether the existing antiviral drugs are effective in the treatment of associated viral infections. Patients with SARS or MERS have been treated with IFN, lopinavir-ritonavir, ribavirin, and corticosteroids[56,57] but the effectiveness of some drugs is controversial.[58]

The efficacies of five antiviral drugs, approved by the Food and Drug Administration, including penciclovir, ribavirin, nitrazine, chloroquine, narfamos, and two renowned broad-spectrum antivirals, favipiravir (T-705), and remdesivir (GS-5734), targeted at COVID-2019 (isolated in vitro), were evaluated.[13] Standard assays were performed to quantify the effects of the drugs on the virus yield, cytotoxicity, and infection rate.[57] As these drugs, being employed in patients with safety track records, were effective against various diseases, it was recommended that they should be evaluated in 2019-nCoV patients.[59] Tables 1 to 3 show the flowchart of the diagnosis and treatment of COVID-19 at the outpatient and inpatient of the Deputy of Public Health of the Islamic Republic of Iran.

10 | PROPOSED TREATMENTS FOR COVID-19

The destructive mechanism of the virus is divided into four main categories, upon which, appropriate treatments can be performed and disease progression prevented. The mechanisms (Figure 1) consisting of the overactive immune cells, stimulation of virus entry into the cell through ACE2 receptor uptake, severe oxygen deprivation, and oxidative stress will be discussed below. The use of acquired immunodeficiency syndrome (AIDS) and pneumonia vaccines may also be considered as suggested preventative treatments.

10.1 | Immune modulators

The immune system is another important target of the COVID-19 virus, and plays a role in immune dysfunction through lymphopenia, and the release of IFN-γ, tumor necrosis factor-α, interleukin-2, CD_4^+ T cells, and cytokines.[60,61] On the other hand, overactivation of the immune mediators, including T cells, by the influenza virus leads to severe pneumonia, and the use of corticosteroids improves the respiratory function.[62] Therefore, early use of immune modulators may prevent acute lung injury and fatal pneumonia induced by COVID-19. CellCept (*Mycophenolate mofetil*), corticosteroids, Plaquenil (chloroquine), and Aralen (hydroxychloroquine), cyclosporine, Stelara (ustekinumab), and Rituxan (rituximab) are immune modulators with different mechanisms that are currently being tried in COVID-19 therapy.

TABLE 1 Inpatient treatment regimens

(a) Dual-drug regimen
The proposed antiviral regimen for the treatment of hospitalized cases includes:
Hydroxychloroquine/chloroquine + clotra (lopinavir/ritonavir) or (atazanavir/ritonavir)
(1) Two 200 mg hydroxychloroquine sulfate tablets or two 250 mg chloroquine phosphate tablets (equivalent to 150 mg baseline) single dose (one dose)
(2) Clotra tablets (lopinavir/ritonavir) 200/50 mg every 12 h two pcs for at least 5 d
*The duration of treatment, depending on the patient's clinical response, can be increased to 14 d.
In the case of gastrointestinal complications, patients with a history of disorders of cardiac rhythm or a high risk of drug interactions may use atazanavir/ritonavir instead of clotra (lopinavir/ritonavir)
*Tablet (atazanavir/ritonavir) 300/100: one daily tablet with food for at least 5 d
If started (atazanavir/ritonavir), 200 mg twice daily (400 mg daily) of hydroxychloroquine will continue until the end of treatment
(b) The triple-drug regimen
If any of the following symptoms occur, severe illness should be considered: consciousness reduction, RR ≥ 24 BP < 90/60, multilobular infiltration (CXR/CT scan), persistent hypoxemia hydroxychloroquine/chloroquine + clotra (lopinavir/ritonavir) or (atazanavir/ritonavir) + ribavirin
(1) Two 200 mg hydroxychloroquine sulfate tablets or two 250 mg chloroquine phosphate tablets (equivalent to 150 mg baseline) single dose (one dose)
(2) Tablets (lopinavir/ritonavir) clotra 200/50 mg every 12 h two pcs for at least 5 d
(3) Ribavirin 1200 mg tablets/capsule every 12 h (every 12 h six pcs) for at least 5 d
*The duration of treatment depending on the patient's clinical response can be increased to 14 d
The duration of treatment depending on the clinical response of the patient can be increased to 14 d
Patients with a history of cardiac rhythm disorders or high risk of interference if they do not tolerate gastrointestinal complications
Medication can be used instead of (lopinavir/ritonavir) clotrazase (atazanavir/ritonavir)
*Tablet (atazanavir/ritonavir) 300/100 one tablet daily with food for at least 5 d
If started (atazanavir/ritonavir), 200 mg twice daily (400 mg daily) of hydroxychloroquine will continue until the end of treatment
*It is noted that the simultaneous administration of cholera and chloroquine can lead to cardiac complications (such as arrhythmia), so caution should be exercised in this regard

TABLE 2 Doses of medicine in specific populations

Medicine	Children	Patients with renal failure	Patients with liver failure	Pregnancy
Hydroxychloroquine	3 to 5 mg based on body weight (in one or two divided doses)	No need to adjust the dose	No need to adjust the dose	Allowed
Lopinavir-ritonavir	230 mg/m^2 body surface (twice daily)	No need to adjust the dose	No need to adjust the dose	Allowed
Ribavirin	5 mg based on body weight In two divided doses	Creatinine clearance 30-50 mL/min—50% of recommended dose Creatinine clearance 15-30 mL/min—25% of recommended dose Creatinine clearance <15 mL/min and dialysis patients—200-400 mg daily	It is not recommended in advanced liver failure (Child-Pugh class C)	Contraindicated
Atazanavir/ritonavir	Children under 15 kg are not recommended In children 15 to 35 kg 50/50 mg and children over 35 kg quasi-adult dose	It is not recommended in advanced renal failure and dialysis patients	It is not recommended in advanced liver failure (Child-Pugh class C)	Allowed
Saltamivir	Infants—3 mg based on body weight twice daily Children <15 kg—30 mg twice daily Children >15-23 kg—40 mg twice daily Children >23-40 kg—40 mg twice daily Children >40 kg—similar to adult doses	Creatinine clearance 30-60 mL/min—75 mg daily Creatinine clearance <30 mL/min—30 mg daily or 75 mg every other day Dialysis patients: 30 mg for regular dialysis and 75 mg for flax filters, three times a week after dialysis	No need to adjust the dose	Allowed

TABLE 3 Medical treatment of pregnant women with coronavirus

(1) Outpatient drug treatment for high-risk cases
This treatment can only be recommended for a pregnant mother who is at risk (with specific illness or immunodeficiency)
Hydroxychloroquine sulfate tablets 200 mg or chloroquine phosphate tablets 250 mg (equivalent to 150 mg baseline) every 12 h for a minimum of 5 d
2. Double drug treatment
Two 200 mg hydroxychloroquine sulfate tablets or two 250 mg chloroquine phosphate tablets (equivalent to 150 mg baseline) single dose (one time)
Clotra tablets (Lopinavir/ritonavir) 200/50 mg every 12 h 2 pcs for at least 5 days or tablets (atazanavir/ritonavir) * 300/100 days one pcs for at least 5 d
*If started (atazanavir/ritonavir), continue with 200 mg twice daily hydroxychloroquine (400 mg daily) until the end of treatment.

10.2 | ACE2 inhibitors

As mentioned above, coronavirus needs to bind to ACE2 to enter into the cells; therefore, blocking virus entry can prevent its complications. High blood pressure medications,[42] including, benazepril, zofenopril, perindopril, trandolapril, captopril, enalapril, lisinopril, and ramipril might block the ACE2 receptors and prevent the virus from entering the cell.

Angiotensin II acts through two G protein-dependent receptors: AT1 and AT2.[13] Angiotensin receptor blockers have no effect on AT2, but inhibit ACE and decrease angiotensin II production. The AT1 receptor stimulation promotes embryonic development, therefore, the use of ACE2 and angiotensin II receptor blocker inhibitors during pregnancy should be prohibited. In late pregnancy, AT2 receptors stimulate abnormal growth and decrease fetal growth.[63,64] The precise role of the AT2 receptor in adulthood is unclear. Angiotensin II inhibitors have their specific medicinal and nutritional supplements, which should be taken concomitantly with renin-angiotensin-aldosterone system blockers, diuretics (especially potassium-sparing diuretics), NSAIDs, anticoagulants, cyclosporine, dipeptidyl peptidase 4 inhibitors, and potassium supplements.[65,66]

Aspirin and other NSAIDs, such as ibuprofen (Advil, Children's Advil/Motrin, Medipren, Motrin, Nuprin, PediaCare Fever, etc), indomethacin (Indocin, Indocin-SR), and naproxen (Anaprox, Naprelan, Naprosyn, Aleve) may decrease the blood pressure lowering effects of ACE2 inhibitors.[67,68] Hence, it is recommended not to prescribe NSAIDs during the outbreak of COVID-19.

10.3 | Antioxidant therapy

Oxidative stress and the consequently related pathways are important mechanisms for lung injury and inflammation.[69,70] Overproduction of free radicals results in oxidative stress that could damage DNA, proteins, and lipids, and other important intracellular organelles.[71] Vitamin C, vitamin E, magnesium sulfates, melatonin, pentoxifylline, nitric oxide, and beta-carotene are antioxidants that inhibit the damages induced by oxidants.[72] Enhancing the function of glutathione and catalase promotes the deactivation of the free radicals.[73,74]

10.4 | Treatment of pneumonia

One of the symptoms clearly visible symptoms in the end-stage patients is the shortness of breath due to hypoxia.[75] Three hypotheses have been suggested for this condition; either the cells cannot extract oxygen from hemoglobin, or hemoglobin cannot bind to oxygen in the lungs for transfer to the cells. The third hypothesis is the lack of capacity of epithelial cells to receive oxygen due to severe pulmonary inflammation. Blood hemoglobin should be measured for appropriate treatment; oxygen therapy, treating for anemia, and immune modulators. The spectrum of bronchodilators used in patients with symptoms of shortness of breath or pneumonia includes arformoterol, aminophylline, ipratropium bromide, tiotropium bromide, theophylline, metaproterenol, terbutaline, salmeterol, and salbutamol.

10.5 | HIV medications

As in HIV, white blood cells are decreased in COVID-19 patients[76]; the recommended drug treatment in COVID-19 patients may be similar to AIDS, but the mechanisms of action of AIDS and corona are completely different.[77,78] Potent broadly neutralizing antibodies (bNAbs) could be a potential treatment along with combination antiretroviral therapy against COVID-19 as recommended for the treatment of AIDS; bNAbs have the ability to suppress viremia and T-cell immunomodulation.[79]

10.6 | Pneumococcal vaccine

As mentioned earlier, the most important complication of COVID-19 is pneumonia.[14,80] The pneumonia vaccine can be used to prevent lung damage.[81] Two new vaccines are recommended to prevent pneumonia, PCV13 (pneumococcal conjugate vaccine), and PPSV23 (pneumococcal polysaccharide vaccine); protecting against 13 and 23 strains of pneumococcal bacteria, respectively. Both vaccines protect against illnesses like meningitis and bacteremia.[82] Although these vaccines protect the body against pneumonia-causing bacteria, the use of these vaccines is a good option as there is no definitive and approved treatment for the COVID-19 virus.[83] PPSV23 strengthens specific antibodies that enhance opsonization, phagocytosis, and killing pneumococci by leukocytes and other phagocytic cells. The level of antibodies associated with protection against pneumococcal disease is not clearly defined.[84] PCV13, composed of conjugated

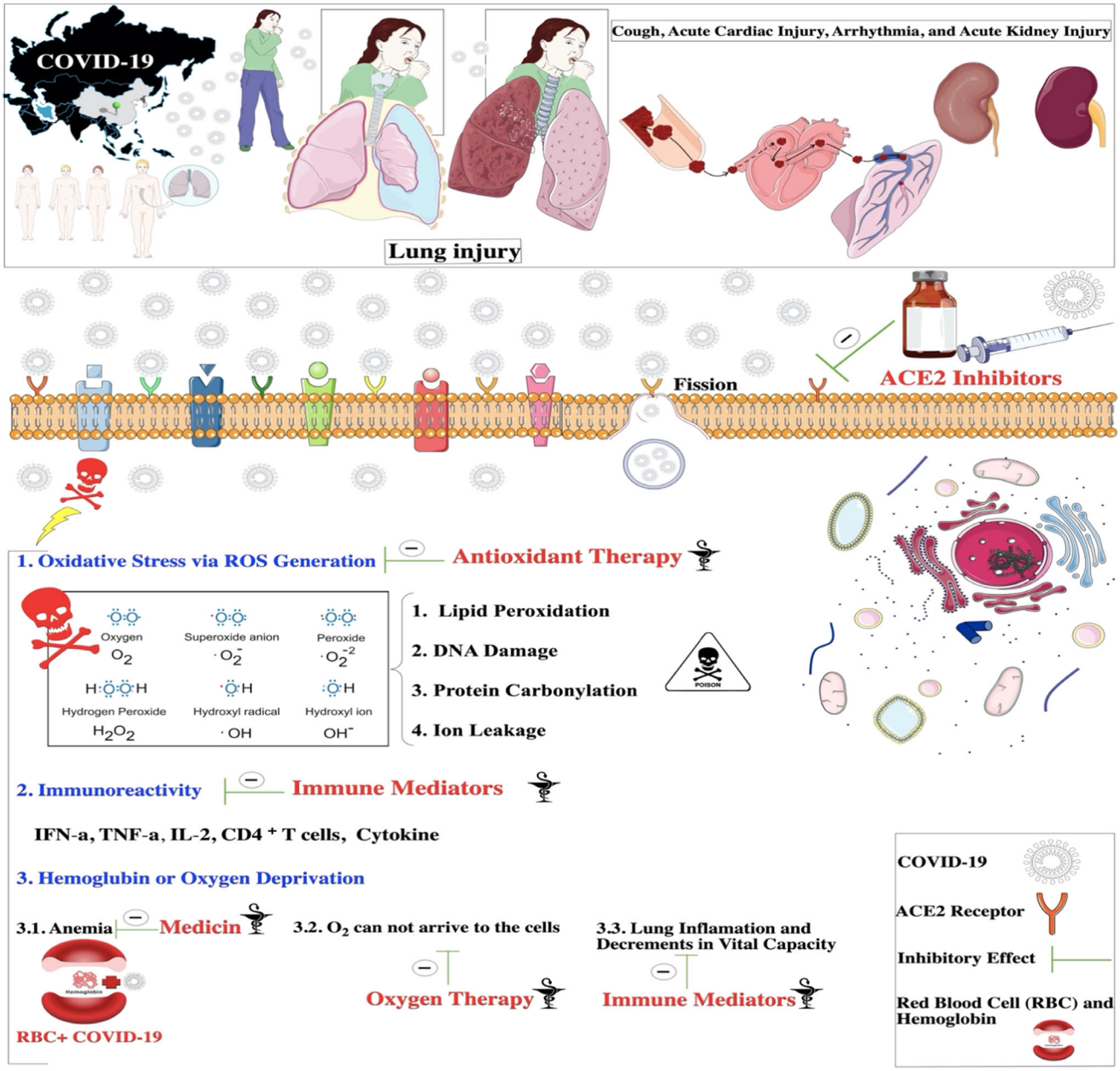

FIGURE 1 A schematic representation of the most prominent routes involved in the COVID-19. Oxidative stress, immunoreactivity, and deprivation of hemoglobin and oxygen are precisely interconnected with the COVID-19 through the angiotensin-converting enzyme 2 (ACE2) receptor. In this review, the effects of well-known suitable medicines against oxidative stress, immunoreactivity, and hemoglobin and oxygen deprivation related routes are discussed. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor

pneumococcal polysaccharides to a carrier protein (CRM197), provides a T cell-dependent immune response. Protein carrier-specific T cells provide the signals needed for maturation of B-cell response. Trial and clinical data support opsonophagocytic activity, as measurable opsonophagocytic enzyme (OPA) activity, as an aid to protection against pneumococcal disease.[85,86] OPA antibody testing provides the ability of serum antibodies to kill pneumococci by promoting complementary phagocytosis and is believed to reflect the protection of pneumococcal disease in the body's internal mechanisms.[87]

11 | FOOD AND SUPPLEMENTATION

Pasteurized dairy products, meat, well-cooked substitutes, entrees, soups (all kinds of cooked entrees and soups), fruits (berries, kiwi, etc), nuts, vegetables, bread, grain, well-cooked cereal products, beverages, and desserts are among the foods and supplements that can boost the immune system[88] and may decrease coronavirus infection. Vitamin C[89] and vitamin D have been suggested as preventative measures for cold and flu. Whether they have the ability to enhance the immune system to fight against COVID-19 needs more

investigation. Vitamin D supplementation may modulate the functionality of the immune system. The use of vitamin D in the treatment of acute pulmonary inflammation has also been suggested and its deficiency plays an important role in the progression of pulmonary diseases.[90] It has also been recommended that individuals should drink plenty of water to keep hydrated as it might help the body to fight against various kinds of infections.

In a few studies, edible ACE2-inhibitor supplements have been reported to reduce the incidence of the virus; they include; two varieties of ginger (*Zingiber officinale* Roscoe), glycyrrhizin and baicalin, scutellarin, hesperetin, and nicotianamine.[91]

In general, none of the supplements, including vitamin C, zinc, selenium, vitamin D, vitamin A, curcumin, ginger, ginseng, vitamin B1, or vitamin B6 have a specific role in preventing the new coronavirus. However, in particular, protein, vitamin D, vitamin C, vitamin A, and selenium deficiencies have been implicated in disabling the immune system to fight any infection.[91] Therefore, it is recommended to prescribe these supplements only for people with micronutrient deficiencies. Care should be taken to avoid overconsumption of these supplements.

Green, oolong, and black tea are also rich sources of antioxidants. It is also recommended to add one spoon of honey and a few drops of lemon to soothe a sore throat.[92] Garlic is recommended as another immune booster which may result in less common colds; spice up your foods with garlic. Many studies have demonstrated that ginger fights against inflammation and it also relieves nausea and stomach ache. Meanwhile, many practitioners of traditional medicine recommend turmeric as a valuable additive with high antioxidant potential.[93] However, further studies are required to confirm these findings.

12 | TRADITIONAL CHINESE MEDICINE

Traditional Chinese medicine (TCM) has played an important role in the treatment of various diseases.[94] Chinese herbal medicines have been suggested for the prevention and treatment of COVID-19 "Recommendations for diagnosis and treatment in TCM (sixth edition)."[95] Other combinations have been suggested by Luo et al.[96] Clinical studies of severe cases of coronavirus have shown that the combined use of lopinavir/ritonavir (Kaletra), arbidol, and Shufeng Jiedu Capsule (a TCM) improved individuals and eliminated the symptoms of pneumonia in individuals.[97]

13 | TREATMENT ON SIGNS/SUPPORTIVE TREATMENT

Other factors that can be considered in the treatment of coronavirus are treatments based on the symptoms created by each individual after the development and involvement of the target tissues. The symptoms may be different in different individuals. There is no specific cure for this infection and the principle of treatment is supportive measures.[75,98]

14 | CONCLUSIONS

Given the condition of the individuals at risk for developing COVID-19, the underlying disease(s), and the mechanism of action of the virus; one can focus on more appropriate drug therapy. In addition to supportive care in patients with COVID-19, the use of a pneumonia vaccine that activates the T and B immune cells may be a good suggestion to prevent the complication of pneumonia. The four main mechanisms of COVID-19 action can be considered as key points for treatment; ACE2 inhibitors, immune modulators, antioxidant therapy, traditional herbal medicine, and oxygen therapy/anemia therapy may be suggested as therapeutic protocols. The appropriate diet can also prevent some of the side effects.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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