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REVIEW ARTICLE

Covid-19's rampage in the human body

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Abstract

The Covid-19 (or Coronavirus Disease-19) was first detected in Wuhan, in the Hubei Province of China. Its causative agent got named as SARS-CoV-2 (or Severe Acute Respiratory Syndrome Coronavirus- 2) in 11 February, 2020 by the International Committee on Taxonomy of Viruses (ICTV). This virus is observed to infect the respiratory system in most patients. In this review, the aim was to discuss the potential of SARS-CoV-2 of affecting almost all the major organ systems of the body and to highlight the importance of interaction between spike glycoprotein of the virus and ACE2 receptor on a host cell. An analysis was made on the gfindings of the different kinds of manifestations of Covid-19 and 42 resources, including: scientific articles and websites, were used for writing this review. The resources were searched on the internet based on a set of keywords. In this review, first the pathophysiology and manifestations of the virus, based on target organ, are discussed. Later, the underlying mechanisms of infection for these organs are compared and a conclusion is drawn. Finally, few of the research works in progress were listed, which help highlight the importance of spike-ACE2 interactions. The result found was that: SARS-CoV-2 is capable of severely affecting: Central nervous system, Respiratory System, Skin, Eyes, Excretory system, Gastrointestinal system, Liver, Circulatory system and Reproductive system. The common mechanism of cellular entry of the virus has been observed to be: Interaction between spike glycoprotein with the ACE-2 receptor. While, many groups are currently conducting research based on this topic, hardly a hand few drugs have been approved for use. Thus, the conclusion is that: research should be focused on developing an approved, potent drug or therapy to inhibit the spike glycoprotein-ACE2 receptor interaction in order to tackle the raging pandemic.

Keywords

Clinical manifestations; Covid-19; SARS-CoV-2; Spike glycoprotein; ACE-2 receptor; Spike-receptor interaction

Introduction

A novel respiratory infection was discovered in December, 2019 in and around a seafood market in Wuhan, China. This market is known to sell live animals like snakes, frogs, bats and rabbits [1]. This virus was found to be a zoonotic virus which is capable of crossing species barrier, from animals to humans. In the year 2003, the Chinese population was infected with SARS (Severe Acute Respiratory Syndrome). The analysis of isolates from the infected patients have identified the virus as a novel coronavirus. Bats hold large range of coronavirus and a large number of studies show that novel coronavirus had originated from bats [2].

The most common symptoms of this disease include: fever, tiredness, cough, difficulty in breathing etc. The new coronavirus causes respiratory tract infections and hence is also called as a Respiratory Virus. This can spread through the droplets produced during cough, sneeze or discharge from the nose and even from the droplets of saliva [3].

Coronavirus belongs to the family: Coronaviridae, RNA viruses with positive sense (5'-3') single stranded RNA as its genetic material. It consists of a helically symmetric nucleocapsid. Coronavirus is the largest among all the RNA viruses with a genome size of approximately 26-32 kilobases. The virus consists of projections called spikes on their surface. Peplomer, spike glycoproteins are present on the surface of this novel virus and these protrusions bind only to certain receptors on the host cells [4]. WHO named this new disease as COVID-19 where 'CO' stands for 'Corona' which in Latin means 'Crown' (crown-like appearance under the microscope due to the spike projections on the surface), 'VI' stands for 'Virus', 'D' stands for 'Disease' and '19' represents the year of first case recorded, that was 2019[5]. The Covid-19 is also referred to as the 2019 novel coronavirus (or 2019-nCoV) [6].

2. SARS-CoV-2 at a glance

2.1 Spike protein

SARS-CoV-2 encodes 27 proteins in total, out of which, 15 are non-structural, 4 are structural and 8 are auxiliary. The outer structure of the virion contains 12 spike glycoproteins (or S glycoprotein) which are involved in the virus-host interactions. These spike proteins contain about 1273 amino acids in them. The spike proteins have an N-terminal (or amino terminal) S1 subunit and a C-terminal (or carboxyl terminal) S2 subunit. The S1 subunit serves as the Receptor Binding Domain and contains around 200 amino acid residues.

The S1 can further be divided into 2 subdomains:

Core subdomain: Leads to formation of S trimers.

External subdomain: This contains 2 exposed, superficial loops which bind with a host receptor called the Angiotensin Converting Enzyme 2 Receptor (ACE2 Receptor) [7].

The amino acid sequence motif contained in the spike protein was stated by authors, at CPC Scientific, to be: KRSFIEDLLFNKV [8], wherein each alphabet represents a specific amino acid. KRSFIEDLLFNKV represents: Lysine, Arginine, Serine, Phenylalanine, Isoleucine, Glutamic Acid, Leucine, Leucine, Phenylalanine, Asparagine, Lysine and Valine respectively. This sequence is a highly conserved epitope that proteolytically activates cleavage and host cell entry. It remains exposed on the surface and contains S1/S2 cleavage sites. This site is cleaved by serine proteases separating the S1 and the S2 regions of the spike protein [9].

2.2 ACE2

ACE2 is a type I transmembrane metallocarboxypeptidase which is mainly expressed in the vascular endothelial cells, renal tubular epithelium and the Le ydig's cells. It breaks down Angiotensin II to Angiotensin 1-7. It negatively regulates the Renin-Angiotensin System. It is assumed that the SARS-CoV-2 gains entry into host's cells by means of its interactions with the ACE2 receptors [10].

2.3 Host-immune reactions

SARS-CoV-2 triggers the expression of numerous Interferon -Stimulated Genes (IFGs). IFGs cause severe hypercytokinemia [11]. The virus enters the body through the respiratory pathway. It infects the epithelial cells and the antigens from these infected cells activate the lung resident Dendritic Cells (rDC). The rDCs migrate to the

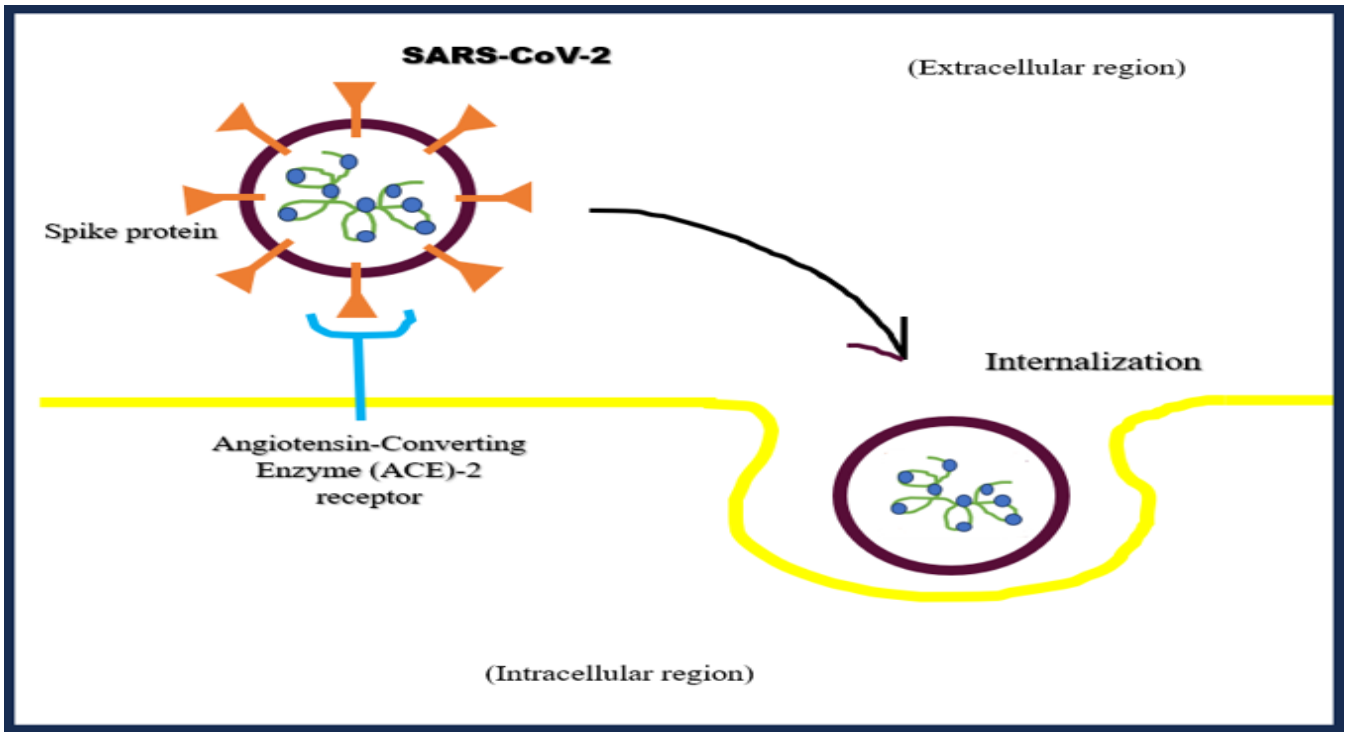

Figure: The diagram illustrates the mechanism of entry of SARS-CoV-2 into a cell via Spike protein-ACE-2 receptor interaction.

draining lymph nodes (DLNs), after getting activated. The T cells in the DLNs recognize the antigens (Major Histocompatibility or Peptide complexes) on the rDCs. The T cells get activated and they proliferate and migrate to the infection sites. Upon arriving at the target sites, the T cells secrete, in large amounts: Cytokines- Interferon-ϒ & Tumour Necrosis Factor-α; Chemokines- CXC Chemokine Ligand-9, 10 & 11; Cytotoxic molecules- Perforin and Granzyme B. The cytokines inhibit viral replication directly and increase antigen presentation. The chemokines recruit more numbers of innate and adaptive cells to fight the virus. The cytotoxic molecules directly kill the infected cell to check further spread of the infection [10].

Recent research data from China has revealed that there is a reduction in the amount of CD4+ and CD8+ (where 'CD' stands for: 'Cluster of Differentiation') T cells in the peripheral blood of Covid19 patients. It has also been observed that there is an increase in the highly proinflammatory CCR6+ Th17 (C- Chemokine Receptor + T Helper 17 cells) among CD4+ T cells. There was also an increase in the number of cytotoxic granules in the CD8+ cells. In severe cases, lowered IFN-ϒ production by CD4+ cells and disturbances in T Regulatory cells were noted. In other words, it was concluded that SARS-CoV-2 induces Lymphocytopenia in the peripheral blood of the host, although the exact mechanism is still unknown [10].

The Covid-19 infection also causes severe cytokine storms at the sites of infection. The types of cytokines involved are: TNF-α, Interferon-Inducible Protein 10, Interleukin-6, Interleukin-8, Interleukin-1β, IFN-ϒ and Monocyte Chemoattractant Protein-1-α. These storms lead to tissue destruction as they hyper activate macrophage/ monocyte lineage cells [10].

Lastly, there is also production of anti-SARS-CoV-2 IgG antibodies in the late acute stage of the infection [10].

3. Pulmonary manifestations

The virus can spread through inhaling the infected air or by touching coronavirus infected surfaces and then touching eyes, nose or mouth. This helps the virus to pass along the mucous membrane into the throat. The Covid-19 goes more deeply than the common cold virus. Respiratory tract is mostly prone to this disease, specifically the lower respiratory tract (trachea, bronchi, bronchioles and alveoli) [12], as it consists of many ACE-2 receptors and makes the Spike glycoprotein interaction with receptor binding proteins Angiotensin -converting enzyme (ACE-2) on membrane receptors helping the virus enter the human cell [13].

Alveoli functions in transporting oxygen into the red blood cells. The infection of alveoli disturbs the oxygen and carbon dioxide exchange, the blood wouldn't receive enough oxygen needed for rest of the body resulting in shortness of breath (Dyspnoea). The lungs are inflamed, heavy with mild pleural effusion of clear serous fluid i.e., Pneumonia leading to Pulmonary Oedema and extensive consolidation (lungs filled with fluid more than air). A study showed that all patients infected with SARS-CoV-2 showed Diffuse Alveolar Damage (DAD) and hyaline membrane formation i.e., membrane composed of dead cells and proteins lining the alveoli. All these result in moderate to severe difficulty in exchange of gas [14].

Acute respiratory distress syndrome starts a few days later. This is a damage of blood vessels in alveoli and accumulation of debris leading to severe shortness in breathing, fast heart rate, dizziness and sweating. Patients are often unable to breath on their own without the help of a ventilator. Computed Tomography scan of a SARS-CoV-2 infected patient's chest shows some patchy areas called "ground-glass opacity" [15].

4. Ocular manifestations

In many case reports, ocular manifestations are seen in patients infected with SARS-CoV-2. Covid-19 damages the conjunctiva membrane, that lines the inside of the eyelid, covering the front part of the eyeballs, resulting in Conjunctivitis. Redness and eye-watering might last for 1-3 weeks. The conjunctival hyperaemia is the initial symptom of Covid-19 positive patients. Usually, ocular manifestations are seen in the middle phase of the disease and in patients suffering with severe pneumonia. The transmission of the virus might occur from ocular surfaces (conjunctiva) to a new host with ocular mucosa, tears and subsequent fomites. The RT-PCR reactions on the conjunctival swabs have been found to be positive for Covid-19, for a small number of samples. Few studies show that SARS-CoV-2 has low prevalence in spreading via conjunctival secretions and tears. Usually patients with Covid-19 show ocular anomalies, acute follicular conjunctivitis (unilateral or bilateral), conjunctival hyperaemia, chemosis, epiphora and increased eye secretions [16].

Some theories suggest that pathophysiology for ocular manifestations might occur through direct inoculation of the ocular tissues from viral particles in droplets or aerosols or migration of the virions from the nasopharynx to the ocular tissues, via nasolacrimal duct or spread from the blood through the lacrimal gland [17].

5. Effects on the central nervous system

Clinical data from across the world have come up with evidence that a large number of Covid-19 patients show symptoms similar to those who have intracranial infections. The symptoms include: headache, epilepsy, disturbed consciousness and a sudden loss of smell or taste. The Beijing Ditan Hospital, in China, has reported a case of viral encephalitis caused by the SARS-CoV-2. Researchers have also detected its presence in the Cerebrospinal Fluid through the method of genome sequencing. This finding provided us with solid evidence of viral encephalitis induced by Covid-19. Patients often present the symptoms of hypoxia and viremia. An autopsy report has revealed the presence of oedema in the brain tissue. These two findings, coupled with the previously observed symptoms of headache, disturbed consciousness and other brain dysfunctions provide evidence that Covid-19 can cause acute toxic encephalopathy [18].

Critically ill Covid-19 patients show high levels of D

dimer and low levels of platelet count [18]. D-dimer is a degradation product of cross linked fibrin resulting from plasmin cleavage. These findings provide evidence that SARS-CoV-2 can lead to the development of acute cerebrovascular diseases [19].

Research on the confirmed mechanism of action of the SARS-CoV-2 on the CNS is still in the process. However, the works done so far provide us with four possible pathophysiological processes of Covid-19 on the CNS.

5.1 Direct viral injury of nervous tissue

SARS-CoV-2 follows the trans-synaptic propagation from the olfactory epithelium. It may also enter the CNS via the systemic circulation by exploiting the ACE-2 receptors expressed on the endothelial cells of the blood vessels in brain. Yet another route of entry involves a blood brain barrier region damaged by cytokine action [20].

5.2 Hypoxia injury

The virus enters the lung tissues and leads to hypoxia over a certain period of time [21]. Such a condition often leads to hypoxic brain injury due to reduced blood flow followed by depletion in energy source. This in turn leads to hypoxic ischemia which may cause highly damaging infarcts affecting areas such as- hippocampus, cerebral cortex etc [22]. These things manifest in the form of impaired cognition, cerebral microhaemorrhages and encephalopathy [23].

5.3 Immune injury

The virus first gains entry into the blood of the host. The viral particles reproduce in mononuclear macrophages throughout the entire body. Then they are released into the blood for a second time. At this time, cytokines, specifically Interleukin-6, are produced in large amounts, through the activation of glial cells, which increase the permeability of the blood-brain-barrier to the viral particles. In vitro experiments have provided evidence that glial cell activation by corona viruses causes secretions of IL-6, IL-12, IL-15 and TNFα, in large amounts [18].

5.4 ACE2

It has been detected that the brain expresses ACE2 receptors over glial cells and neurons. When the virions reach the cerebral blood circulation, it undergoes a sluggish movement, as is the nature of the blood flow in the region. This retarded pace facilitates the interaction of the spike protein with the ACE2 receptors. This initiates a cycle of viral budding and inflammations in the region [24].

6. Haematological manifestations

Numerous Covid-19 patients have shown conditions of Covid-19 Associated Coagulopathy (CAC), Disseminated Intravascular Coagulopathy (DIC) and thrombosis. The findings have showed the presence the of symptoms like: DAD, thrombotic microangiopathy of small vessels & capillaries in lungs, megakaryocytes within pulmonary capillaries with nuclear hyperchromasia & atypia, partially degenerated neutrophils entrapped in fibres, endothelial cell injury, diffuse microvascular thrombosis, deep vein thrombosis [25], pulmonary embolism, ischemic stroke, myocardial infarction, acute large vessel occlusion, large vessel arterial thrombosis, cardioembolic events and systemic arterial events [26].

In the initial stages of CAC, D-dimer and fibrin/fibrinogen degradation products' levels rise up. In later stages, prothrombin time, partial thromboplastin time and platelet count abnormalities occur [27].

The complete genomic sequence of SARS-CoV-2 has revealed the presence of 7 Open Reading Frames (ORFs), surface, envelope, membrane and nucleocapsid proteins [28]. It is theorized that initially, the structural and the non -structural proteins, respectively, attack the porphyrin ring of Haemoglobin. Simultaneously, 3 ORFs: ORF1ab, ORF10 and ORF3a make a coordinated attack on the 1-β chain of haem. This reduces the oxygen or carbon dioxide carrying ability of the molecules. As more and more haemoglobin molecules get rendered ineffective, respiratory distress appears. Tissues get damaged and capillaries get easily broken due to inflammation. Fibrinogens fill the cracks in the capillaries leading to coagulopathy, finally leading to thrombosis. However, whether this theory is correct, remains to be confirmed by further experimentation [29].

On the other hand, some researchers also attribute the process of development of CAC to tremendous IL-6 storms and spike protein's affinity to ACE2 receptors, as these factors directly lead to the formation of thrombosis [25].

7. Cutaneous manifestations

Findings have showed that the Kawasaki disease is one of the signs in Covid-19 infected patients. Another skin manifestation termed "Covid toes'' has also been reported. In addition to the common symptoms of Covid-19 like dyspnoea, inflammation and fever, patients have also shown erythematous rash and pseudo-chilblains in kids and young adults [30].

As Covid-19 shows asymptomatic conditions for 14 days after infection, these lesions might serve as indicators for infection. The entry of viral particles to the blood leads to lymphocytic vasculitis (damage of blood vessels in the skin). The virus does not target the keratinocyte but the immune response to the infection makes a way for Langerhans' cell activation and creates a state of vasodilation and spongiosis. Livedo reticularis is due to accumulation of micro thrombosis produced from different organs reducing the flow of blood to the cutaneous microvasculature system. Intravascular coagulation and accumulation of deoxygenated blood in venous plexus thought to be the causative mechanism of such manifestations. Pauci-inflammatory thrombogenic vasculopathy with the accumulation of C5b-9 (terminal complement complex) and C4d (complement protein 4d) are also helpful in these studies [31].

Some theories suggest the possibility of endothelial vasculature injury and S glycoprotein-ACE2 receptor interaction in the endothelial cells [31].

8. Gastrointestinal and hepatic involvement

The gastrointestinal symptoms presented by Covid-19 include: diarrhoea, vomiting and abdominal pain. SARS-CoV-2 RNA was detected in the stool of the patients, during

the course of illness, by the process of reverse transcriptase PCR. Diarrhoea is one of the earliest symptoms of Covid-19 and may even appear before the development of any respiratory distress [32].

Covid-19 patients have also been detected with liver injury with raised levels of enzymes in the blood. Abnormal levels of alanine aminotransferase, aspartate aminotransferase and a slight elevation in serum bilirubin levels were detected. Other hepatic changes were found to be micro vesicular steatosis and mild lobular activity [32].

Some studies claim that the interaction between the viral spike protein and host ACE2 receptors may result in diarrhoea. A recent study has revealed that ACE2 are highly expressed in the glandular cells of the gastric and duodenal epithelia and proximal and distal enterocytes. These cells get invaded by the virus resulting in: malabsorption, unbalanced intestinal secretions and activated enteric nervous system. These events finally result in diarrhoea. This also results in an altered "gut-lung axis" [33].

The mechanism of liver injury is not fully understood but it is assumed that the probable causes could be: viral infection of the hepatocytes or immune-related injury or drug hepatotoxicity. It is also hypothesized that the virus may invade the cholangiocytes through the ACE2 interaction mechanism leading to malfunctioning of liver function [32].

9. Nephrological manifestations

Acute renal impairment is seen in SARS patients. The virus binds to the ACE-2 receptors and infects the cells of the kidney, and the virus invades and makes copies of it leading to the tissue damage. The signs shown by the kidney are high protein levels in urine and abnormal blood work. Abnormal low levels of oxygen in blood impair the functioning of kidneys. To protect the body from viruses the immune system rushes the cytokines. Thus, this heavy rush creates severe inflammation and destroys the healthy tissues including the kidney. Tiny clots are formed in the bloodstream. The impact of coronavirus on kidneys is unclear. However, the heart, lungs, liver, kidneys functions are dependent so the damage of one organ might risk the other parts too [34].

10. Reproductive system involvement

There has been a recent report of a Covid-19 patient complaining of testicular pain [35]. A recent study has also shown impaired male gonadal function and reduction of Testosterone: Luteinizing Hormone level ratio, in the serum [36]. There is also a high expression of ACE2 in the ovaries, vagina, placenta and the uterus, which makes these potential target sites of SARS-CoV-2 [37].

There is very little insight into the pathophysiological progression of Covid-19 in the reproductive system. However, the high expression of

Table. The given table summarizes Covid-19's effects on the different body parts or systems and its corresponding causative mechanisms (pathophysiology)

AFFECTED SYSTEM	SYMPTOMS	CAUSATIVE MECHANISM
Respiratory System	Dyspnoea, pneumonia, pulmonary oedema, DAD, hyaline membrane formation, ARDS, fast heart rate & dizziness.	***S glycoprotein-ACE2 receptors interaction in the lower respiratory tract.***
Eyes	Inflammation of the conjunctiva, conjunctival hyperaemia, follicular conjunctivitis (unilateral or bilateral), chemosis, epiphora, increased eye infections and other ocular secretions.	***Working theories: Infection through droplets/ aerosols or migration from nasopharynx or spread from blood.***
Central Nervous System	Headache, epilepsy, disturbed consciousness, sudden loss of smell or taste, viral encephalitis, hypoxia, viremia, acute toxic encephalopathy, acute cerebrovascular diseases & other brain dysfunction.	***Axonal transport/ hypoxia injury/ IL-6 storms/ S glycoprotein-ACE2 receptor interactions in glial cells & neurons.***
Circulatory System	CAC, DIC, DAD, thrombotic microangiopathy, megakaryocytes in pulmonary capillaries, neutrophils trapped in fibres, endothelial cell injury, diffuse microvascular thrombosis, deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, acute large vessel occlusion, large vessel arterial thrombosis, cardioembolic events & systemic arterial events.	***Working theories: Breakdown of 1-β chain of haem by viral particles/ cytokine storms/ S glycoprotein-ACE2 interactions.***
Skin	Kawasaki disease, Covid toes, erythematous rash & pseudochilblains in kids & young adults, maculopapular exanthem, papulovesicular rash, urticaria, acral red purple papules, livedo reticularis lesions, petechiae, different kinds of skin lesions and lymphocytic vasculitis.	***Working theories: Endothelial vasculature injury/ S glycoprotein-ACE2 receptor interactions in the endothelial cells.***
Gastrointestinal System & Liver	Diarrhoea, vomiting, abdominal pain, abnormal levels of enzymes in blood, micro vesicular steatosis and mild lobular activities.	***Hypothesis: S glycoprotein-ACE2 interactions in glandular cells, gastric & duodenal epithelia, proximal & distal enterocytes/ viral infection of hepatocytes/ hepatotoxicity/ immune injury of the liver.***
Excretory System	High protein levels in urine, abnormal blood work, inflammation of the kidneys and tiny clots in the bloodstream.	***S glycoprotein-ACE2 interactions in the cells of the kidney.***
Reproductive System	Testicular pain in men.	***Hypothesis: S glycoprotein-ACE2 interactions in the testes, ovaries and uterus.***

ACE2 in the testes, ovaries, vagina, placenta and the uterus, has made the researchers suspect the role of spike protein-ACE2 receptor interaction as the causative mechanism [37].

11. Works in progress

Bojadzic et al. have reported that Methylene blue is capable of inhibiting the spike-ACE2 interactions [38]. Dalbavancin has been proved to be able to bind to ACE2 receptors in animal models and thus effectively blocking cellular entry by SARS-CoV-2 [39]. Ledipasvir (a drug used to treat Hepatitis C) and Evans blue have been predicted to have high affinity for ACE2 receptors. The same group has also reported high affinity of Evans blue and Irinotecan for the receptor binding domain of the spike glycoprotein [40]. Bisoxatin (used for treating constipation and preparing colon for surgeries) has been reported to bind at the interface of spike-ACE2 [41]. Chloroquine and Hydroxychloroquine (anti-malarial drugs) have been reported to interact with some of the spike protein binding domains of ACE2 receptors [42].

Conclusion

Covid-19 is not merely a flu. It is a deadly disease, which holds the potential to cause multi-organ damage or failure. Such widespread damage could turn out to be very dangerous, in the long run, even after recuperation. Hence, we desperately need a clear-cut cure for this disease.

The interaction of spike glycoprotein with the ACE2 receptors is the primary mechanism which helps SARS-CoV -2 in invading the cells of lungs, kidneys, CNS, GI system, liver, blood, reproductive system, eyes and skin. It is often seen that higher the abundance of ACE2 receptors on target tissues, easier it is for the virus to infect the said tissue. Hence, it is a crucial mechanism with regards to developing a cure for Covid-19.

There are quite a few research groups which are currently perusing this line of work, but only a hand few drugs have been approved for use. Thus, much greater amount of emphasis must be laid on further research to establish an approved, potent drug or therapy to reduce or inhibit the spike protein-ACE2 receptor interactions.

Authors' contributions

AB conceived the review. SS and VA collected the literature and wrote the manuscript. AB, helped in the original draft. AB critically reviewed the initial draft and streamlined the idea. SS and VA prepared and revised the tables and figures and AB helped in revision of the manuscript. All authors carefully read, revised, and approved the manuscript for submission.

Compliance with ethical standards

Conflict of interest: The authors declare no conflict of interest.

Ethical issues: None.

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