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A REVIEW ON SMALL MOLECULES AND PEPTIDES FOR THE TREATMENT OF COVID-19.

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ABSTRACT

Corona virus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11th 2019, and it has caused 400 million of cases and a million deaths since then. Researchers from various fields of expertise around the world are attempting to identify the novel molecules as well as most appropriate drugs, which are already known to treat other diseases which could address the process by which SARS-CoV2 invades and replicates in human cells as well as potentially improve cytokine storms and other related complications. In this article, we focus to look on the most promising drugs that could play a significant role in this treatment of COVID-19. The review discusses the currently explored molecules with a focus on RNA-dependent RNA polymerase (RdRp) inhibitors such as the nucleoside analogues remdesivir, favipiravir, and ribavirin. Inhibitors of 3C-like protease (3CLpro), papain-like protease (PLpro), and other potentially novel molecules like TMPRSS inhibitors, Inhibition of endocytosis Inhibition E, M, N & accessary proteins, and Suppression of excessive inflammatory responses, describing their potential targets, activities, clinical status, and side effects.

KEYWORD: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), corona virus disease 2019 (COVID-19), small molecules, TMPRSS inhibitors, clinical trials.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) is a member of a large family of viruses called coronaviruses. These viruses can infect people and some animals. SARS-CoV-2 was first known to infect people in 2019. The virus is spread from person to person through droplets released when an infected person coughs, sneezes, or talks. It may also be spread by touching a surface with the virus on it and then touching one's mouth, nose, or eyes, but this is less common. Currently the researchers are working on development of small molecules or exploration of currently available drugs for prevention and treatment of SARS-CoV-2.[1]

The COVID-19 is caused by the novel virus SARS-CoV2, has clinical symptoms ranging from asymptomatic, moderate pneumonia to significant acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS).[2]

In the advent of the devastating COVID-19 pandemic in 2019 there have been 452,201,564 confirmed cases of COVID-19, including 6,029,852 deaths, reported to WHO till 12 March 2022.[3]

Academic laboratories and drug discovery groups all around the world are working feverishly to identify small molecules, peptides and antibodies that can prevent the spread and treat SARS-CoV-2 in humans. It is critical to first recognize therapeutic targets and then develop and analyse small molecules and biologics capable of successfully engaging these targets and inhibiting the spread of disease.[4]

Types of coronaviruses

The SARS-CoV-2 is a novel corona virus, and it shares 79.5 percent of its DNA with the SARS-CoV that caused the 2003 SARS outbreak. SARS-CoV-2 is a part of the coronaviruses (CoV) family. Electron microscopy of CoV revealed that it is essentially a positive-stranded RNA viruses with a crown-like structure on the surface, which imply its name as Coronaviruses.[5,6] These

'crown-like structures' are glycoproteins found on the viral envelope that assist virus entrance into host cells.[7] Coronaviruses are categorized into different subfamilies as follows: Alpha coronavirus, Beta coronavirus, Gamma coronavirus, Delta coronavirus and omicron.[8] Although the zoological development of coronaviruses is still being studied, it is widely acknowledged that Alpha- and Beta coronaviruses predominate in bats and rodents, whilst birds species are the source of Delta- and Gamma coronavirus gene sources.[9,10,11]

CoV Genome Structure and Replication

The CoVs genome is a positive-sense RNA (+ssRNA) molecule with a single strand, with the genome size between 27 and 32 kbp, making it one of the largest known RNA viruses.[12,13] CoVs have at least six open reading frames in their genome (ORFs). The initial ORFs (ORF1a/b) are positioned at the 50th end of the genome, accounting for almost two-thirds of the total length, and encode a polyprotein1a, 1b. (pp1a, pp1b).[14]

Other ORFs found on the 30th end encode at least four structural proteins: The envelop glycoprotein spike (S) oversees detecting host cell receptors. Membrane (M) proteins are responsible of structuring the virions. The envelope (E) proteins are responsible of virus assembly and release. The nucleocapsid (N) proteins play functions in pathogenicity as an interferon (IFN) inhibitor as well as in the packaging of the RNA genome and virions.[15,16]

In addition to the four primary structural proteins, there are species-specific structural and accessory proteins such as HE protein, 3a/b protein, 4a/b protein.[13]

The viral genome is a positive-sense RNA genome, it translates into two polyproteins, polyprotein 1a(pp1a), polyprotein 1b (pp1b) once it enters the target cell's cytoplasm. These polyproteins degrade into 16 non-structural proteins (NSPs), which merge to form the replication-transcription complex (RTC), which is involved in genome transcription and replication. As a result, RTC uses discontinuous transcription to create a nested set of sub-genomic RNAs (sgRNAs).[13]

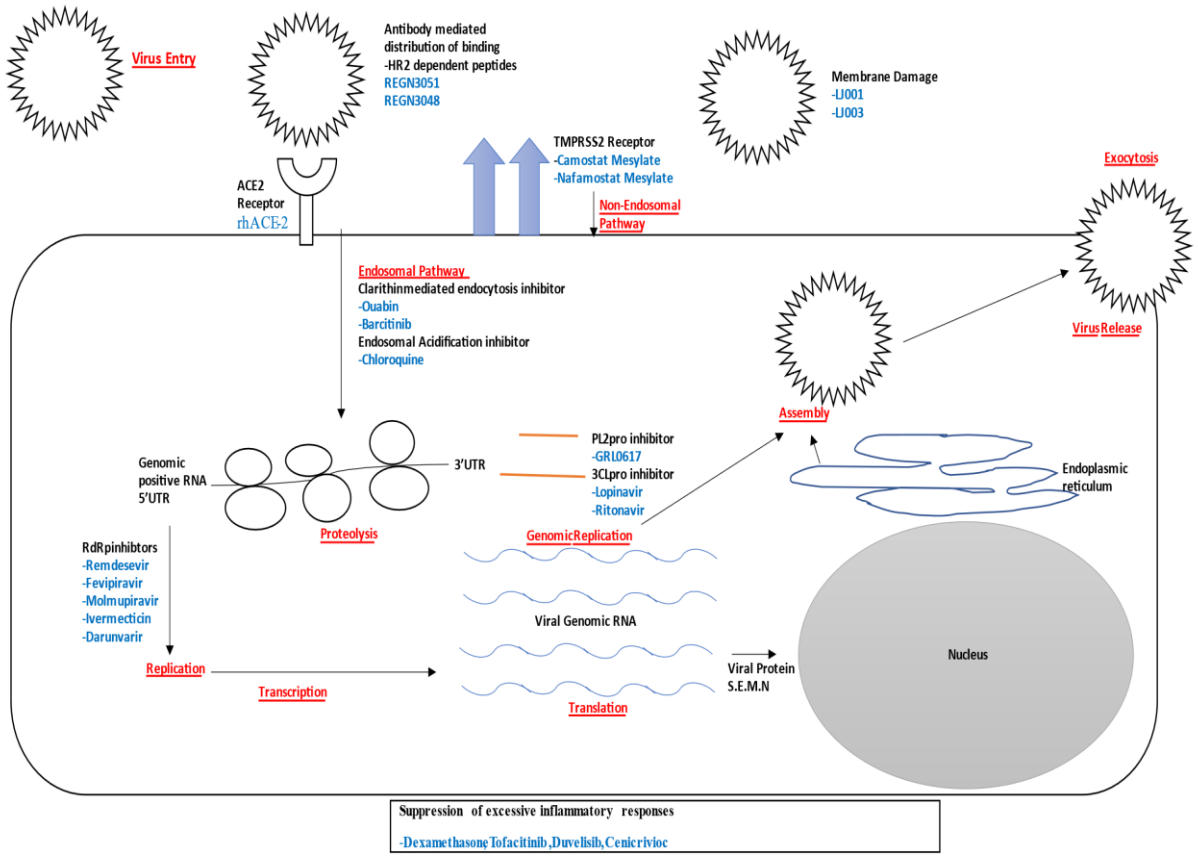


Fig 1: life cycle of SARS-CoV-2. Along with the mechanism of currently available drugs at different targets.

Various drug targets related to covid-19

1. Inhibition of SAR-CoV-2 entry/fusion
2. Inhibition of endocytosis
3. Inhibition of viral enzyme
4. Inhibition of viral envelope, membrane, nucleocapsid and accessory protein
5. Suppression of excessive inflammatory responses

Inhibition of SAR-CoV-2 entry/fusion

SARS-CoV-2 infects ciliated bronchial epithelial cells and type II pneumocytes, where it binds to the surface receptor angiotensin-converting enzyme 2 (ACE2) via the S glycoprotein present on virus surface.[17,18,19] When S glycoprotein attaches to ACE2, the cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin cleave trimer S protein. S glycoprotein is made up of two subunits: S1 and S2. S1 controls the host range and cellular tropism of the virus, as well as facilitating viral attachment to target cells. S2 unit facilitates the fusion of viral and cellular membranes, allowing viruses to enter the cell via endocytosis.[17]

The affinity of the virus's surface proteins for ACE2 receptors is a critical step in viral entrance. Understanding the mechanism of SARS-CoV-2 transmission could lead to new insights into viral transmission and the identification of treatment targets. According to a recent study, the affinity between S glycoprotein of SARS-CoV-2 and ACE2 binding efficiency is 10–20 fold higher than that of SARS-CoV, which could explain SARS-extremely CoV-2's infectious potential.[20]

To enter the host cells, SARS-CoV-2 utilizes the spike protein presents on the viral surface. Receptor binding domain (RBD) of the spike protein is a critical target for antibody mediated disruption of binding.[21]

ACE-2 receptors are present on the cell surface of bronchial epithelial cells. So, delivering an excess of soluble ACE-2 helps neutralize the virus, by competitively binding to SARS-CoV-2. (rhACE-2)[22]

TMRSS2 facilitate the entry of virus in host cell. Inhibition of TMPRSS-2, blocks entry of virus in host cell. Camostat mesylate and Nafamostat mesylate are the example of TMPRSS inhibitor.[23]

Inhibition of endocytosis

Inhibition of endocytosis is another potential strategy towards developing drugs. In humans Clarithin mediated endocytosis is regulated by AP-2 associated protein kinase 1 (AAK-1).[24] Oubain is inhibitor of clathrin-mediated endocytosis, is being tested for its efficacy in drug trials for SARS-CoV-2 positive patients.[25] Recently, Chloroquine and its derivative hydroxychloroquine have been reported to prevent endocytosis of SARS-CoV-2 in human[27] and had been used as a therapy against SARS-CoV-2 infection.[26] Also, it was shown in vitro, that hydroxychloroquine (EC50 = 0.72lM) is far more potent in inhibiting SARS-CoV-2 infection than Chloroquine (EC50 = 5.47 lM).[27,28] These both drugs are discontinued from the clinical trial.

Inhibition of viral enzyme

There are many drugs which acts against viral protease, polymerases and hydrases.[29] There are two types of RNA-dependent RNA polymerase (RdRp) inhibitors: nucleoside drugs and non-nucleoside drugs. Non-nucleoside inhibitors are susceptible to drug resistance and exhibit an inability to act on other subtypes, which limits their development. In contrast, nucleoside drugs have the advantages of directly acting on highly conserved active pockets and acting as catalytic substrates for RdRp. At present, the primary representative nucleoside RdRp inhibitors for COVID-19 are remdesivir, favipiravir, ribavirin, and penciclovir. Although these inhibitors have different indications, their mechanisms of action are same. These inhibitors are all prodrugs that are converted into the corresponding active structure (triphosphate structure) in the host cell and are incorporated into the RNA chain by RdRp. This incorporation causes a fatal mutation or terminates immature RNA chain synthesis.[29]

Lopinavir and ritonavir is protease inhibitors that targets 3C like protease, responsible for processing the polypeptides.[30] The papain-like protease PLpro is an important coronavirus enzyme that is required for processing viral polyproteins to generate a functional replicase complex and enable viral spread. Recent reports of newly identified inhibitors of SCoV2-PLpro could lead to the rapid development of novel anti-COVID-19 therapeutics with dual effects—blocking SARS-CoV-2 spread and promoting antiviral immunity in the host.[31]

Inhibition of viral envelope, membrane, nucleocapsid and accessory protein

SARS-CoV-2 envelope (E), membrane (M), and nucleocapsid (N) proteins are essential for virus survival and propagation therefor, they are the ideal therapeutic targets. Because these viral proteins are physically different from host proteins, drugs targeting these proteins will have negligeable side effects.[32,33]

The N protein decreases RNA silencing and RNA interference induced by siRNA. As a result, several siRNA-based treatments target viral E, M, and N protein translation and, at least in vitro, suppress viral replication. However, because to intrinsic stability concerns and the lack of dependable delivery techniques, siRNA-based medicines are currently not ready for human use. Hexamethylene amiloride inhibits the E protein's ability to function as an ion channel.[4]

Another chemical inhibitor, PJ34, targets the N protein's specific ribonucleotide-binding region at the N-terminus. It is crucial to note that the majority of these inhibitors were created to combat the SARS virus; however, due to modifications in the SARS-CoV-2 virus, such inhibitors may be less effective in combating the ongoing COVID-19 pandemic.[34]

LJ001 and LJ003 are broad-spectrum antiviral drugs that not only prevent viral entry into host cells but also cause singlet oxygen molecules to be produced by the viral

membrane.[35] LJ001, on the other hand, is physiologically unstable and photo-dependent and, establishes a new family of antiviral drugs.[4]

Suppression of excessive inflammatory responses

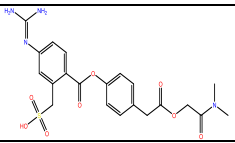
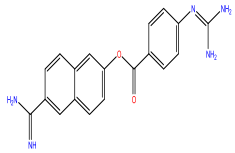
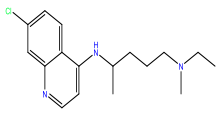
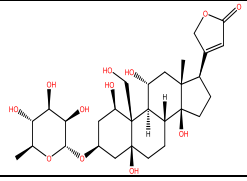
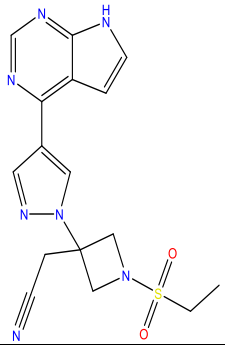
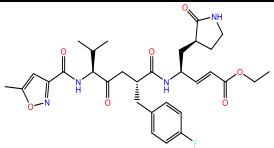
A well-coordinated cytokine response is essential for the host immunological response. Some SARS-CoV-2 infected individuals have been found to have a hyper-inflammatory response, probably due to a dysregulated cytokine response. It has been found that COVID-19 patients in the ICU had increased levels of cytokines in their plasma than non-ICU patients, implying that cytokine dysregulation is implicated in the severe form of COVID-19 disease.[36,37]

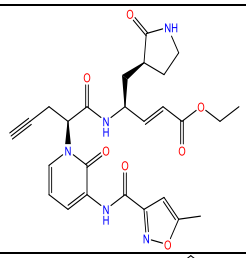
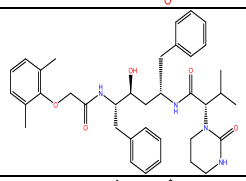
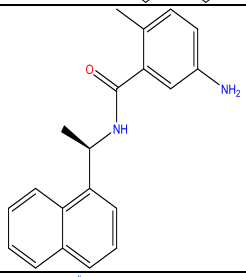
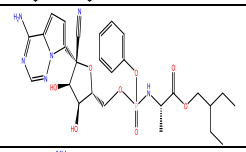
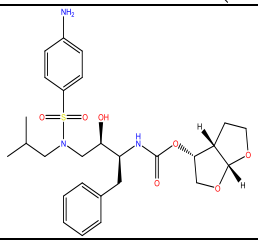
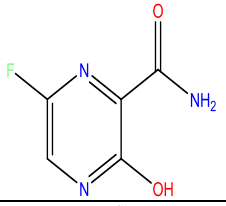
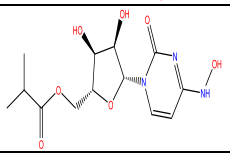
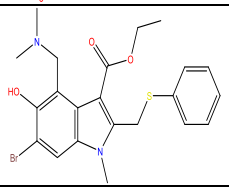
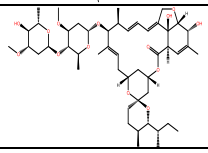
Corticosteroids have a high pharmacological potential for reducing systemic inflammation. However, their use in COVID-19 patients is still questionable and necessitates further research. Tocilizumab, an IL-6 receptor-specific antibody, is currently being tested in a multicentred, randomized, controlled clinical trial.[38]

Convalescent plasma treatment is another recent improvement in COVID -19 treatments. With infection rates rising and no specific treatment available, convalescent plasma (CP) therapy has been advocated as a primary treatment. In this therapy, plasma taken from a disease-free donor is utilized to establish humoral immunity against patients infected with SARS-CoV-2.[39]

The donor patient's plasma serves as a source of human antibodies against the illness. However, large-scale human trials are needed to thoroughly investigate and evaluate CP as a therapy option for COVID-19.[40]

Table 1: Small molecules for the treatment of covid-19.

Targeted viral compounds	Examples of drugs	Mechanism of action	Status of approval	Structure	Reference No.
Inhibition of SARS-CoV-2fusion/entry					
TMPRSS	Camostate mesylate (fovipan™)	TMPRSS2 inhibitor that blocks the TMPRSS2-entry pathway (interferes viral entry)	Approved in Japan		[23]
	Nafamostat mesylate (buipel™)	It is much more potent than camostat in the blockade of S-protein-mediated SARS-CoV-2 entry.	Approved in Japan		
Inhibition of endocytosis					
Endosomal acidification	Chloroquine	An antimalarial that sequesters protons in lysosomes to increase the intracellular pH.	Discontinued		[40]
Clathrin- medited endocytosis	Oubain	ATP1A1- binding steroids; inhibits clathrin-mediated endocytosis	Preclinical		[41]
	Baricitinib	AP-2 associated AAK1 inhibitor	FDA approved		[42]
Inhibition of viral enzymes					
3 CL pro					
Peptidomimetic 3CLpro inhibitors	AG7088 (Rupintrivir)	Inhibits 3CLpro activity	Discontinued		[29]

	AG7404	Inhibits 3CLpro activity	Phase 1		[29]
Nonpeptidic 3CLpro inhibitors	Lopinavir	Inhibits 3CLpro activity	FDA approved		[43]
PL pro	GRL0617	Inhibits PLpro activity	Preclinical		[44]
RdRP	Remdesivir	Nucleotide analogue; inhibits viral RNA synthesis	FDA approved		[45,46]
	Darunvarir	Inhibits SARS-CoV-2 protease for proteins cleavage	FDA approved		[47]
	Favipiravir	Binds to the viral RdRp and inhibits it.	Investigational		[48]
	Molnupiravir (MK-4482, EIDD-2801)	Inhibits the replication of SARS-CoV-2	Phase 3		[49,50]
	Umifenovir (Arbidol™)	Inhibition of membrane fusion of viral envelop and Clarithin mediated endocytosis.	Investigational		[51]
	Ivermectin	Inhibits SARS-CoV-2 replication	FDA approved		[52]

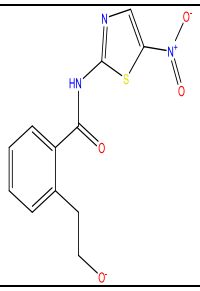
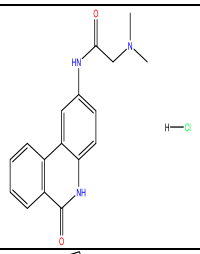
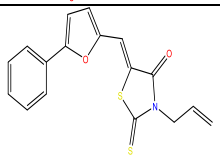
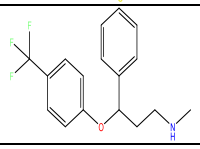
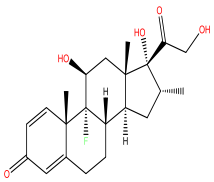
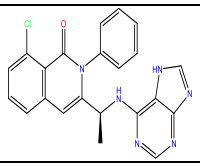
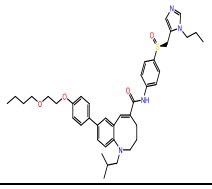
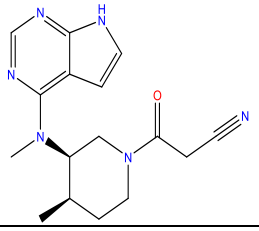
	Nitazoxanide	It impairs the posttranslational modification of viral protein	Phase 3		[53]
Inhibition E, M, N & accessary proteins					
N protein	PJ 34	Impairs viral replication	Preclinical		[54]
Membrane & Accessory protein	LJ001	Induces membrane damage	Preclinical		[55]
	LJ003	Induces membrane damage	Preclinical		[55]
Suppression of excessive inflammatory responses					
	Dexamethasone	Dexamethasone reduced deaths in approximately one third of patients requiring ventilation and by one fifth in those requiring oxygen.	Phase 4		[56]
	Duvelisib	Inhibition of PI3K	Phase 2		[57]
	Cenicrivioc	Cenicrivioc is dual inhibitor of the chemokine receptors CCR2 and CCR5, which is responsible for inflammation.	Phase 2		[58]

Table 2: Antibodies/peptides/RNA under the clinical trial for the treatment of covid-19.

Targeted viral compounds	Examples of antibodies/peptides	Mechanism of action	Status of approval	Structure	Reference No.
Inhibition of SARS-CoV-2fusion/entry					
RBD of the S1 subunit of S	REGN3051 & REGN3048 mAbs	Antibodies target the RBD domain of the S1 subunit	Preclinical		4
S2 subunit of S	HR2P & P1 peptides	Antiviral peptides that inhibit fusion of S with host cell receptor	Preclinical		4
	rhACE-2	Increase the circulating level of ACE-2	Phase 2		59
Inhibition E, M, N & accessary proteins					

E & M protein	Si RNA	Short chains of dsRNA that interfere with the expression of SARS-CoV protein	Preclinical		60
Suppression of excessive inflammatory responses					
	Tofacitinib	IL-6 receptor-specific antibody	Phase 3		61

CONCLUSION

Since the emergence of the COVID-19 pandemic, scientists worldwide have been committed to the research and development of SARSCoV-2 therapeutic drugs. Currently, wide variety of research is going on for treatments worldwide but due to the rapid emergence for research many of the efforts lack organizing and randomized clinical trials and remain on the level of evidence about their ability to fight COVID-19. Potential SARS-CoV-2 inhibitors have been discovered through the use of computer simulation techniques, such as molecular docking and free energy calculations. Based on the highly conserved replicated gene sequence of SARS-CoV-2, the development of anti-SARS-CoV-2 or broad-spectrum antiviral drugs targeting RdRp, 3CLpro, PLpro, TMPRSS2, S protein and ACE2 might constitute a future research direction.

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