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Targets of Modern Drugs and Therapeutics for COVID-19: A Review

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ABSTRACT
Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is a member of genus-*Betacoronavirus* with positive sense single stranded RNA and structural proteins (S, M, E and N) is causing severe health problems to the individuals of almost every country. Healthcare systems of almost every country are facing huge challenge everyday with increasing number of COVID-19 patients. As there is no effective vaccine or perfect medicine for treatment of SARS-CoV-2 infected patients, only some clinical managements (e.g. prevention of infection, supportive care) and antiviral agents are weapons against COVID-19 today. We have summarized the drugs, therapeutics and their mode of action at molecular level. Traditional medicines used by different countries (e.g. China) are also included in this review. We have also discussed the steps of CoVs life cycle and the points of drug targets to prevent, control and treat the patients of the COVID-19, as the therapeutics or drugs will be effective until the arrival of approved vaccine and specific drug/ drugs to cure the SARS-CoV-2 infections.

KEY WORDS: SARS-CoV-2, COVID-19, *Betacoronavirus*, Traditional medicines.

I. INTRODUCTION

Today whole civilization is standing in front of a single word COVID-19 (Corona Virus Disease-2019). In 1940's corona virus was firstly identified [1, 2] and after about 20 years later in 1960's the first Human Corona Virus (HCoV) was identified with very mild respiratory infections, later they named as i) Human CoV 229E (HCoV-229E) and ii) HCoV OC43 [3-5]. Later another four different Human corona virus were discovered-HCoV- Hong Kong University 1 (HKU1) HCoV-NL63, Severe Acute respiratory Syndrome Corona Virus (SARS-CoV), Middle East Respiratory Syndrome Corona Virus (MERS-CoV) [6, 7]. Now the newly discovered corona virus is SARS-CoV-2 (which is the main concern of the present world), phylogenetic analysis clearly indicated that SARS-CoV-2 virus genome is 88% identical with two Bat derived SARS like corona viruses i) bat-SL-CoVZC45 and ii) bat-SL-CoVZXC21 (reported from eastern China in 2018) and 96.2% sequence similarity with BatCoV RaTG13 (a Bat corona virus detected in *Rhinolophus affinis* from Yunan province of China. SARS-CoV-2 virus exhibit about 79% sequence similarity with SARS-CoV and MERS-CoV [8]. Among the seven corona viruses, HCoV-229E, HCoV-OC43, HKU1 and HCoV-NL63 are responsible for the one third of common cough and cold disease in human [9]. In very rare cases they cause pneumonia, bronchitis in children, old individuals, individuals with chemotherapy, HIV (Human Immunodeficiency Virus) and in immunocompromised patients [10-15]. Along with the respiratory symptoms the enteric and neurologic diseases are also very common [16-20]. In 2002-2003, 32 countries were affected with SARS-CoV and confirmed reported cases were- 8422, out of which 916 patients died with 10-15% of mortality rate [21]. Initially Palm Civets were considered as source of main origin of SARS-CoV [22], but later phylogenetic studies supported the Bat origin of SARS-CoV virus (as the DNA sequence was similar with Bat originated virus) [23].The SARS-CoV was firstly reported from Guandong of China. In 2012-2013 another virus of the same family MERS-CoV came in headlines of Saudi Arabia [22, 24, 25]. In 2015 republic of Korea faced the same virus (MERS-CoV) with 1401 confirmed cases among them 543 individuals were died (with high mortality rate-39%), in Saudi Arabia the mortality rate was 37% [26, 27]. Although the clinical symptoms of MERS-CoV and SARS CoV are same spreading pattern of these two viruses are different and MERS-CoV transmission was in a particular geographical region only [28]. All the MERS-CoV affected individuals were reported from Middle

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Eastern countries (either directly or from travel history) [29, 30].

China health authority reported World Health Organization (WHO) about the several Pneumonia cases with unknown aetiology from Wuhan of Hubei province of China central in 31st of December 2019 [31]. The affected individuals are mostly related to the Hunan wholesale Seafood market [31]. In January 1st week, the virus was firstly collected from throat swab of a patient and WHO named the virus 2019-nCoV (novel corona virus) [32] later the corona virus study group named this virus as SARS-CoV-2 [33] and the disease related to this virus was named as Corona Virus Disease-2019 or COVID-19. In 30th January 2020 WHO declared SARS-CoV-2 as a Public Health Emergency of International Concern (PHEIC) [34].

Today corona virus (SARS-CoV-2) has created alarming situation by spreading from human to human [35] and no vaccine has been developed till date for common people. In this review we have summarized the understanding of SARS-CoV-2 infection, pathogenesis of the COVID-19, diagnosis, treatment, control and prevention strategies as well as the drugs and their point of action at molecular level to combat the corona virus.

II. CLASSIFICATION OF CORONA VIRUS

The family *Coronaviridae* (under the order Nidovirale) is subdivided into two Sub-families- *Coronavirinae* and *Torovirinae* [36] of which *Coronavirinae* Sub-family is divided into four main genera i)Alphacoronavirus ii)Betacoronavirus, iii)Gammacoronavirus and iv)Deltacoronavirus [37]. The genus alphacoronavirus contains strains - HCoV-229E and HCoV-NL63, beta coronavirus contains 5 different strains HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2/2019-nCoV. The gamma corona virus is the corona viruses from birds and whales and the delta corona virus is reported from pigs and birds (Table-1) [38, 39]. We have also summarised the cellular receptors and hosts of alpha and beta corona viruses in Table-2.

Table 1:
Classification of Coronaviruses.

Classification of Coronavirus	
Kingdom	Orthornavirae
Phyllum	Pisuviricota
Class	Pisoniviricetes
Order	Nidovirales
Family	Coronaviridae
Sub-family	Coronavirinae
Genus	*Alphacoronavirus*
	Betacoronavirus
	Gammacoronavirus
	Deltacoronavirus

Table 2:
Alpha and Beta coronaviruses their cellular receptors and hosts.

Genera	**Coronavirus strains**	**Discovery in year**	**Cellular receptor**	**Host**
Alphacoronavirus	HCoV-229E	1966	Human Aminopeptidase N (CD13)	Bats [10,40]
	HCoV-NL63	2004	ACE2	Palm Civets, Bats[41,37]
Betacoronavirus	HCoV-OC43	1967	9-O-Acetylated sialic acid	Cattle [42,11]
	HCoV-HKU1	2003	9-O-Acetylated sialic acid	Mice [12,17]
	SARS-CoV	2005	ACE2	Palm Civets, Bats [37,17]
	MERS-CoV	2012	DPP4	Bats, Camels [18]
	SARS-CoV-2/2019-nCoV	2019	ACE2	Bats [8, 23,43]

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III. VIRAL STRUCTURE

The SARS-CoV-2 virus is enveloped with positive-sense-single stranded RNA (+ssRNA) and about 26-32 kb genome size [36, 44]. Electron microscopic analysis clearly indicates that from outside the protein coverings are i) Spike protein (S) a type of glycoprotein I ii) Membrane protein (M) iii) Envelope protein (E), a highly hydrophobic protein iv) Nucleocapsid protein (N), a basic RNA binding protein and V) Hemagglutinin Esterase (HE) glycoprotein [45-47]. S protein plays important role in viral entry into host and activates the host cell immune response [47].

S protein:

The S proteins has three domains i) Ectodomains ii) TM region iii) Intracellular domain region [48]. The Ectodomain (ED) is made up of two parts S1 domain (receptor binding three S1 head) and S2 domain (membrane fusion subunit) on C-terminal [48]. The crown like shape of the virion is due to the arrangement of the S-proteins around the surface of the virus so why the name is given *Corona Virus* [48]. S1 domain is considered as a major antigen that activates the immune response of the host cell [49]. S1 domain's has three major parts- NTD (N-Terminal Domain), CTD (C-Terminal Domain) and the RBD- (Receptor Binding Domain) [50]. S1 domain and host receptor ACE2 interactions and subsequent S2 domain mediated fusion with the host plasma membrane helps entry of the viral genome into the host cell cytoplasm [47]. The 14 amino acids of the RBD and the 18 residues of the ACE2 of host plays important role in viral entry [51]. In this interaction the K341 of host cell's ACE-2 and R453 residue of RBD of virus play the most important role [51].

In Vero F6 cells anti ACE-2 antibody can able to block the entry of the virus and replication [51, 52]. Virus has another way to bind with the host is Dendritic cell specific intercellular adhesion molecule-3, this helps virus to grab the non-integrin or L-SIGN in lymph nodes or in liver (seven glycosylation asparagines linked sites in S protein is main cause for L-SIGN based viral entry into the host cell) [53-55]. Many drug designers have targeted RBD of S protein for the better results (eg. a peptide sequence when similer to RBD sequence inhibit S1: ACE-2 interactions and inhibit the viral entry in Vero cells) [50, 56, 57]. In Vero E6 cells SARS-CoV replication is inhibited when siRNA against S sequence was applied [50, 58].

E protein:

E protein is the smallest TM structural protein size ranges from 8.4-12 kDa plays important role in viral assembly, bud formation as well as viral egress [59]. E protein exhibits higher variability among different viruses of CoV family [59]. This protein has two distinct domains: i) hydrophobic domain and ii) charged cytoplasmic tail [59]. When E proteins oligomerize they form ion channels, but the actual function of the ion channels are not clear [60]. E proteins are gathered near the ER and Golgi body regions [59]. This protein also acts as virulence factor [61].

M protein:

Membrane protein or M protein plays an important role in the determination of the viral shape, incorporation of viral particles into Golgi complex as well in the stabilization of the N (Nucleocapsid protein) [61]. The M protein has three domains with long internal C-terminal domain and external short N-terminal domain [62]. This protein by interacting with the other structural proteins (N and S) plays an important part in viral intracellular homeostasis as well as in viral assembly [61]. M protein interaction with the S proteins inside the ERGIC is necessary for the assembly of the viral progeny [61]. The core of the virus is dependent on the M and N protein interaction which helps to form the RNP complex (Ribonucleoprotein Complex) [61]. The M proteins help in host sensitization by virus as well as activate the kappa (nuclear factor) pathway and IFN-β pathway [63].

N protein:

This protein is highly conserved among the different members of the CoV family [25]. N protein has three Intrinsic Disordered Regions (IDRs): i) N-arm region ii) central linker region and iii) C-tail region. This protein has two terminal domains: N-Terminal Domains (NTD) and C-Terminal Domains (CTD), these two domains are also considered as main structural and functional domains of the N proteins [25]. The main function of CTD and NTD are dimerization and RNA binding respectively [64]. The arginine and serine rich CL region contains large number of phosphorylation sites; also the C-terminal IDRs are important for the oligomerization of the N-protein as well as interaction of N and M proteins [65, 66]. I protein regulates the viral replication and translation and inhibits the host cell protein synthesis

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(translation) by EF1α [64]. It alters the host cellular metabolism, cell cycle of the host and the apoptosis (as N proteins inhibit the CDK4 proteins) [45, 64]. N protein interacts with the viral RNA by ribonucleoside's 5′-monophosphate (AMP, UMP, CMP, and GMP) through its N terminal's RNA binding sites [65]. After knowing this information RNA binding inhibitors were designed like N-(6-oxo-5,6-dihydrophenanthridine-2-yl) (N, N dimethyl amino) (PJ34) using HCoV-OC43 model and H3 (6-chloro-7-(2-morpholin-4-yl-ethylamino) quinoxaline-5,8-dione), which is also inhibit the binding of NTD of N protein to viral RNA [65]. The CTD of N protein has an important role in oligomerization [67]. At 300 µM concencentration C-terminal tail peptide (N377-389) of N protein competes with the oligomerization process [67]. The N220 (Nucleocapsid protein peptide) is able to activate the cytotoxic T cells and high binding affinity to the human MHC-1 in T2 cell [68]. The N220 selectively kill the nucleocapsid protein expressing cells (in transgenic animals) and it is considered as a potential candidate for developing DNA vaccine [68].

HE (Hemagglutinin Esterase):

Among the Beta corona viruses this enzyme is present on the envelope and it is considered as a marker of corona and influenza virus evolution [69]. HE enzyme can reversibly attach with the O-acetylated-sialic-acids [69].

IV. MODE OF VIRAL TRANSMISSION

Initially it was assumed that SARS-CoV-2 viruses are transmitted from animal to human in Wuhan seafood wholesale market [75]. Medical workers and family member clusters have confirmed transmission mode of this virus is person to person via the respiratory droplets released during coughing and sneezing [76]. Fomites may also be a major source of transmission as the survival of the SARS-CoV is up to 96 hours and other Corona viruses surface survival rate is about 9 days (35, 76). One report suggested that hospital transmission rate is about 41% along with high transmission among the health care workers (78). Not only the close person to person contact but also sweat, stool, respiratory secretions and urine can be a mode of SARS-CoV virus transmission [79-81].

V. STEPS OF SARS-COV-2 VIRUS LIFE CYCLE

Step1 (Attachment of virus with host cell): Corona viruses get attached with the help of Spike proteins (S) to the target host cell by interaction with viral cell protein: i) Angiotensin Converting Enzyme-2 (ACE-2) for all SARS-CoV and ii) Dipeptidyl Peptidase -4 (DPP-4) for all MERS-CoV [52, 82].

Some corona viruses enter into the host cell through completely different route i.e. with the help of proteases. Protease dependent virus entry occur through two enzyme activity i) Transmembrane Protease Serine 2 (TMPRSS2) and ii) Airway Trypsin-like Proteases (TMPRSS11D) [83-85]. S protein of virus is activated by these proteases during HCoV-229E and SARS-CoV infection through the cell membrane [84]. Cathepsin L also has been reported as a path for SARS and MERS CoV entry [83].

Step 2 (Entry of Viral mRNA into host cell cytoplasm):

The CoV genome along with its nucleocapsid is entered into the host cell cytoplasm where the two genes (Replicase gene) of viral RNA (ORF1a and ORF1b) are translated with the help of host cell ribosome and protein synthesis machinery to produce two polyproteins (pp1a and pp1ab) [70, 72]. pp1a contains 4382 amino acids and the pp1ab contains 7073 amino acids [86]. These two genes in the 5′- end cover about two third part of the viral genome and the rest one third part viral genome towards 3′- end of the RNA are responsible for the encoding of 4- structural proteins (S,M,E and N) [64]. From 5' to 3' direction the order of the genes present in the CoVs RNA are ORF1a-ORF1b-S-OEF3-E-M-N [87].

Step 3 (Development of replication transcription complex):

The two polyproteins (that are produced in host cytoplasm by hijacking the host protein synthesis mechinary) are auto processed by host and viral proteases to develop 16 Non-Structural Proteins (NSPs) [88-90]. Two proteases or Main proteases (Mpro) i) $3CL^{pro}$ (3-C Like proteases or Chymotrypsin-like cysteine protease) and ii)PL^{pro} (Pappine Like proteases) plays important role in the processing of the two viral polyproteins (pp1a and pp1ab) [91]. The C-terminal end of pp is processed by $3CL^{pro}$ and N-terminal end is processed by PL^{pro} [91]. Out of total 14 cleavage sites first 3 sites cut by PL^{pro} and rest 11 sites cut by $3CL^{pro}$ [92]. $3CL^{pro}$ is present in homodimer form and the active site of this enzyme forms Cys-His diad on active site [93].

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$3CL^{pro}$ dimerization can be inhibited by mutation in Ser139 and phe140 positions [94]. Functions of all pps are given in Table-3.The Non-Structural Proteins (NSPs) assemble to form *replication transcription complex* [95]. The main catalytic core of PL^{pro} contains 316 amino acids and a consensus sequence which is required for the cleaving of the replicase substrate [95]. Zinc and Zinc conjugates are also responsible for the inhibition of the $3CL^{pro}$ and PL^{pro} [96].

Table 3:
The different Non-Structural Proteins (NSPs) of SARS-CoV and their functions at molecular level.

Non-Structural Proteins (NSPs) and their functions			
NSPs	**Functions**	**NSPs**	**Functions**
NSP1,NSP2	Host gene expression [70].	NSP12	RNA Dependent RNA Polymerase [71].
NSP3,NSP5	For multidomain Complex (M protease) helps in replication of viral genome [70].	NSP13	Helicase activity [71].
NSP4, NSP6	Transmembrane proteins [71].	NSP14	Shows Exoribonuclease activity [71].
NSP7, NSP8	Primase [72].	NSP15	Shows Endoribonuclease activity [71].
NSP9	A RNA binding protein (Dimeric protein) [73].	NSP16	Methyletransferase activity [71].
NSP10	Co-factor for activating replicative enzymes [74].	NSP (1-16)	Important role in viral replication and transcription [71].

Step 4 (Corona virus replication transcription and translation):
Initially the full length *viral genomic RNA (+ssRNA)* with the help of viral replicases is *transcribed* to form full length *negative-strand (-ssRNA)* viral RNA template for replication and production of its genomic RNA [97]. The *sub-genomic RNAs* are formed from the full length *negative-strand (-ssRNA)* viral RNA template by RNA Dependent RNA polymerases (RdRp) [98]. These mRNAs will transcribe and translate to form structural (S, M, E and N) as well as accessory proteins [64].

Step 5 (Formation of new virus particles):
The structural proteins (S, M and E) that have been produced are entered into the Endoplasmic Reticulum Golgi Intermediate Complex (ERGIC) and produce the viral envelop [99]. The N protein and the replicated viral genome together form Ribonucleoprotein Complex (RNP) [99]. The outer covering of the virus is formed by three structural proteins M, E and S [99]. Finally the virus particles are released from the ERGIC by forming a bud like structure [100]. The newly formed virions form the vesicle later that will be fused with host cell plasma membrane and released into the extracellular regions [101].

VI. SYMPTOMS AND LABORATORY RESULTS

Among the different symptoms of COVID-19 patients most common are:

i) Dry cough, sore throat and fever with pneumonia (75% case with bilateral pneumonia) [78,102-104].
ii) Septic shock and Acute Respiratory Stress Syndrome (ARDS) [102, 104].
iii) Multiple organ failure with 11% mortality rate [104].
iv) Severe ARDS with lung damage (possible way of entry of SARS-CoV-2 through ACE2 that are densely present on ciliated cells of airway epithelium [102, 104].
v) Many cases with Dyspnoea, myalgia and fatigue chest pain with some less common symptoms of abdominal pain, nausea, and vomiting, abdominal pain with diarrhoea [78, 102].
vi) COVID-19 patient's symptoms are different from SARS-CoV and MERS-CoV (as the SARS-CoV-2 virus exhibit least upper respiratory infection with higher lower respiratory tract infections) [102].
vii) Severe complications like acute kidney and cardiac injury with arrhythmia are also reported in many cases of COVID-19 [102, 104].

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viii) Haemoptysis (coughing up of blood) is also reported in COVID-19 [75].

6.1 Laboratory findings

i) Blood serum of COVID-19 patient exhibit elevated level of proinflammatory cytokines (eg.interleukin-1, IL6, IL12, monocyte chemoattractant protein-1 (MCP1), interferon gamma (IFN γ), IFN induced protein 10 (IP10) and macrophage inflammatory proteins 1A (MIP1A), these all are related to severe damage of lungs and pulmonary inflammation [105].

ii) Cytokine storm (with elevated blood proinflammatory cytokines) are reported in many ICU patient [102]. Anti-inflammatory cytokines (eg. IL10, IL4) are also common in patient with Cytokine storm [102].

iii) Most important finding in COVID-19 is higher infection rate in older adult males than in older adult females and very least infection among children [102,104]. In animal models the infection trend is same (i.e. SARS-CoV-2 infect aged male macaque than younger) [106].

iv) The elevated level of Lactate dehydrogenase, prolonged prothrombin time with lymphopenia is common abnormalities among the patients of COVID-19 [78,104, 107].

v) Some patient of COVID-19 exhibit elevated blood level of creatinin, creatinin kinase, aspertate amino transferase with C-reactive proteins [102,107,76].

vi) Peripheral regions of the lungs of some COVID-19 patient exhibit multifocal, patchy ground-glass opacity in CT-scan report (Computed Tomography) [76]. Also some CT-scan report with consolidative pulmonary opacities and pulmonary parenchymal opacities [102, 104, 107, 108, 78].

VII. TREATMENT OF COVID-19

No perfect antiviral treatment and vaccine for COVID-19 is available till now, only antibiotic treatment (to reduce secondary bacterial infections), oxygen support with life support system is recommended in most of the cases [109, 110].The mRNA (messenger RNA) containing vaccine for developing Corona viruses Spike protein (S) developed by Moderna's vaccine with US NIAID (National Institute of Allergy and Infectious Diseases), they reported 45 study participants and 25 of them exhibit high level of virus recognizing antibodies that are higher or equal to the patient who recovered from COVID-19 . But as the Moderna has not shared its data and lots of data reported that recovered patient's neutralizing antibody levels are not very high, it's not at all clear that the vaccine will enough to protect the humans from SARS-CoV-2[111]. Oxford University of UK also developed a vaccine which has successfully protected six monkeys from pneumonia but, the vaccinated monkeys developed same intensity of virus in their nose as the unvaccinated group [112]. The vaccine made by China with inactivated SARS-CoV-2 virus particles and exhibit more promising antibody response, but with same problem as faced by Oxford University group [113]. In most cases therapeutic treatments of SARS and MERS is utilising for the treatment of COVID-19 patients [114]. Although there is no evidence of a specific drug or combination of drugs that can be used for treatment of COVID-19 patients, several anti-viral drugs are using with some good clinical outcomes. Oseltamivir with antibiotic support and Remdesivir (drug for Ebola virus) is using in many cases to treat the COVID-19 patients [102, 115]. Clinical trials of anti-virus drug Remdesivir against SARS-CoV-2 is now widely utilising in many trials combination with other drugs [116, 117]. Shufeng Jiedu Capsule (SFJDC) with antiviral combination Lopinavir/Ritonavir, Arbidol also used and showed good clinical benefits in many cases [118]. Ribavirin, Ritonavir and Interferon α-2a is also considered as a potent antiviral agent previously used for MERS-CoV treatment [119].In Table 4 several drugs with their targets at the molecular level, in Table 5 different supportive drugs with molecular function and in Table 6 functions of different herbal drugs have been discussed for the treatment of COVID-19 disease.

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Table 4:
Name of drugs or therapeutics and their possible target to control COVID-19 caused by SARS-CoV-2.

Sl No.	Compound name	Targets of Drugs	Target CoVs	Other targets	References
1	Chloroquine	Inhibit viral replication, inhibit glycosylation of the ACE2 receptor and inhibit virus-cell fusion.	SARS-CoV,MERS-CoV,HCoV-229E	Antiviral against Flavivirus, Influenza virus, HIV, Nipha-Hendra virus.	[120-126]
2	Hydroxychloroquine	Antiviral activity by targeting lysosome, elevating the endosomal pH.	SARS-CoV-2	Useful to control graft-versus-host disease in human	[23,126-128]
3	Chlorpromazine	Inhibit viral replication.	SARS-CoV, MERS-CoV, HCoV-229E	Antipsychotic drug for Schizophrenia, inhihibit Clathrin mediated endocytosis,inhibit replication of Hepatic c virus, Alphavirus, Mouse hepatitis virus.	[129-132]
4	Loperamide	Inhibit viral replication.	SARS-CoV, MERS-CoV, HCoV-229E	Antidiarrheal opoid receptor agonist reduce the intestinal motility.	[133]
5	Lopinavir	Inhibit replication.	SARS-CoV, MERS-CoV, HCoV-229E	Anti HIV protease inhibitor,SARS-CoV main protease.	[134]
6	1,2,4-triazole derivative	Inhibit viral NTPase/Helicase i.e, inhibit viral replication	SARS-CoV, MERS-CoV	Not Known	[135,136]
7	K22	Inhibit membrane bound viral RNA synthesis	MERS-CoV	Not Known	[137]
8	Saracatinib	Antiviral activity	SARS-CoV, MERS-CoV, HCoV-229E	Used in tumor malignancies through Src family of Tyrosine kinase inhibition. Antiviral against feline Infectious Peritonitis	[138]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
9	Saracatinib + Gemcitabine	Synergistic Antiviral activity	All CoV diseases	Treatment of cancer	[139,140]
10	E-64-D (Aloxistatin)	Cathepsin inhibitor, block viral entry.	SARS-CoV, MERS-CoV.	Not Known	[141]
11	Triflupromazine	Protein mediated cell	SARS-CoV,	Neurotransmitter	[142]

		cell fusion	MERS-CoV	inhibitor	
12	Fluphenazine	Protein mediated cell cell fusion	MERS-CoV	Neurotransmitter inhibitor	[142]
13	Promethazine	Protein mediated cell cell fusion	MERS-CoV	Neurotransmitter inhibitor	[142]
14	Imatinib methylase	May inhibit viral replication	SARS-CoV, MERS-CoV	ABL-1 pathway inhibitor	[143]
15	Dasatinib	May inhibit viral replication	SARS-CoV, MERS-CoV	ABL-1 pathway inhibitor	[143]
16	Interferon-α, Interferon-β	Inhibit viral replication.	SARS-CoV, MERS-CoV	Increase host immune	[144-147]
17	Cyclopholins	Interacts with nsp1 to modulate calcineurine pathway	SARS-CoV	Not Known	[148]
18	Cyclosporin	Calcineurine inhibitor	Broad range of CoVs	Highly immunosupressive	[148,149]
19	Trametinib,Selumetinib,Everolimus,Rapamycin,	Kinase signaling pathway inhibitor	SARS-CoV, MERS-CoV	Immunopathological interventions	[150,151]
20	Chlorpromazine, Fluphenazine,Promethazine	Inhibit cell cell fusion, inhibit clathrin mediated endocytosis	MERS-CoV	Nurotransmitter inhibitor	[142]
21	ADS-J1	Interruption of MERS-CoV entry	MERS-CoV	HIV entry inhibitor	[142]
22	K11777	Cathepsin (Cystein protease) inhibitor	Inhibit entry of CoVs	Inhibitor of endosomal pathway, inhibit entry of Ebola, Marburg, and Paramyxoviruses viruses	[152-155]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
23	Ouabain, Bufalin	Block Clathrin mediated endocytosis	MERS-CoV	Not Known	[156]
24	N-(2-aminoethyle)-1-aziridineethanamine	Inhibit catalytic activivy of ACE2, and S- mediated cell cell fusion	SARS-CoV	Not Known	[157]
25	SSAA09E2	Inhibit SARS-CoV with host ACE2 interaction	SARS-CoV	Not Known	[158]
26	SSAA09E1	Blocking cathepsin L	SARS-CoV	Not Known	[158]
27	SSAA09E3	Preventing fusion of viral and cellular membrane	SARS-CoV	Not Known	[158]
28	Naphthalene sulphonate derivative	Clathrin inhibitor	CoV cellular entry	Not Known	[159]
29	Tetradecyltrimethy	Dynamin I,II GTPase	HCoV-NL63	Not Known	[159]

	leammonium bromide	inhibitor inhibit viral replication by clathrin mediated entry			
30	Nystatin,Methyle β-cyclodextrin	Inhibit viral entry by Caveolin-1 dependent endocytosis	HCoV-OC43	Cholestero binding or depleting agent	[160]
31	Griffithsin	Binds with viral surface glycoprotein and inhibit CoV entry	Inhibit SARS-CoV in mice	Inhibit Glycoprotein of HIV	[161,162]
32	Hexamethylene amiloride	Ion channel activity is reduced	SARS-CoV, HCoV-229E	Not Known	[163-165]
33	PJ34	Binds to a distinct ribonucleotide binding pocket at the N terminal site of N (Nuleocapsid)	HCoV-OC43	Not Known	[163-165]
34	H3 (6-chloro-7-(2-morpholin-4-yl-ethylamino) quinoxaline-5,8-dione)	Binds to a distinct ribonucleotide binding pocket at the N terminal site of N (Nuleocapsid)	HCoV-OC43	Not Known	[166,65]
35	Catechin gallate and gallocatechin gallate	Inhibits the N terminal site of the nuleocapsid	SARS-CoV	Not Known	[167]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
36	Thiazolidine derivatives (LJ001), and (LJ003)	Produce singlet oxygen molecule and prevent fusion of viral and host cell membrabne	Broad range of CoVs	Not Known	[168-171]
37	Ribavirin, Mycophenolic acid	Nucleic acid synthesis inhibitor	SARS-CoV,MERS-CoV	Not Known	[172,173]
38	Mizoribine	Nucleic acid synthesis inhibitor	SARS-CoV,MERS-CoV	Immunosuppressant	[174]
39	Gemcitabine hydrochloride	DNA synthesis inhibitor	SARS-CoV,MERS-CoV	Chemotherapeutic	[150]
40	Remdesivir	Novel nucletide analog prodrug	MERS-CoV	Treatment for Ebola and Marburg virus	[175]
41	Ribavirin + Ritonavir +Interferon α-2a	Good antiviral activity	MERS-CoV	Not Known	[119]
42	Mefloquine, Amodiaquine, Emetine dihydrochloride hydrate	Antiviral activity	SARS-CoV,MERS-CoV	Antiparasite, Antibacterial	[150,120]

43	Toremifene citrate	Oestrogen receptor1 antagonist	SARS-CoV,MERS-CoV	Not Known	[150]
44	Mycophenolic acid	Inhibit inosine Monophosphate Dehydrogenase	MERS-CoV	Immunosuppressant, inhibit Hepatitis B,Hepatitis C and Arboviruses	[176,177]
45	Silvesterol	Inhibitor of DEAD-box RNA helicase elF4A, inhibitor of cap dependent viral mRNA translation.	MERS-CoV and HCoV-229E	Potent inhibitor of Ebola virus infected Macrophages, inhibit human rhinovirus and poliovirus 1	[178]
46	Alisporivir	Inhibit replication of coronavirus	MERS-CoV, HCoV-229E, SARS-CoV	Not Known	[179]
47	6-markaptopurine,6-thioguanine, N-ethylmaleimide	Inhibitor of MERS -CoV PLpro	MERS-CoV	Not Known	[180]
48	Disulfiram	Allosteric inhibitor of MERS -CoV PLpro	MERS-CoV	Inhibitor of methyletransferase, kinase and urease	[181-183]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
49	8-(Trifluoromethyle)-9H-purine-6-amine	Inhibitor of PLpro	SARS-CoV, MERS-CoV	Anticancer agent, arrhythmia, antiviral activity	[184-186]
50	Naphthalene amides	Inhibitor of PLpro	MERS-CoV	Not Known	[187-190]
51	N-(benzo[1,2,3]triazol-1-yl)-N-(benzyl) acetamido) phenyl) carboxamides , ML300	Inhibitors of CLPro	SERS-CoV	Not Known	[191]
52	ML80-N-(tert-butyl)-2-(N-arylamido)-2-(pyridin-3-yl) acetamides	Inhibitors of CLPro	SERS-CoV	Not Known	[192]
53	Arylboronic acids, quinolinecarboxylate derivatives, thiophenecarboxylate, phthalhydrazide-substituted ketoglutamine analogs	Inhibitors of CLPro	SERS-CoV	Not Known	[193]
54	N3 (PDB ID: 2AMQ)	Inhibitors of CLPro	SERS-CoV	Not Known	[194]
55	Colistin,valrubicin	Inhibit Mpro(Main	CoVs	Not Known	[195]

	,icatibant,bepotastine,epirubicin,epoprostenol,vapreotide,aprepitant,caspofungin, and perphenazine	proteases)			
56	Benzodioxole	Inhibitor of PLpro	SERS-CoV	Not Known	[189]
57	Popyphenols from *B. papyrifera*	Inhibit 3CL and PL CoV protease	SARS-CoV, MERS-CoV	Not Known	[196]
58	Peptide derivative (N3)	Inhibit the proteolytic activity of MERS-CoV 3CLpro	MERS-CoV	Not Known	[197]
59	AG7088 a peptide derivative analogs	Inhibit CoVs by targeting the 3CLpro	Broad range of CoVs	Not Known	[198]
60	Benzotriazile derivatives	Inhibition against 3CLpro	SARS-CoV, MERS-CoV	Not Known	[199]
61	5-Chlioropyridyl esters GRL001	Block replication 3CL pro	SARS-CoV, MERS-CoV	Not Known	[200,201]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
62	Pyrazolone based neuraminidase inhibitor	Inhibit 3CLpro	SARS-CoV, MERS-CoV	Not Known	[202]
63	Pyrrolidine based peptide GC376	Inhibit 3CLpro	MERS-CoV	Not Known	[203]
64	Pyrrolidine based peptide GC813	Inhibit 3CLpro	MERS-CoV	Not Known	[204]
65	Oseltamivir(Tamiflu) + chloroquine+ Favipiravir	Antiviral activity	SARS-CoV	Target neuraminidase on influenza virus (A and B)	[205-207]
66	Umifenovir (Arbidol)	Block the viral and cell membrane fusion, virus endosome fusion,	SARS-CoV 1, SARS-CoV-2,	In influenza virus (A and B) infections and r Arbovirus. Also antiviral against Human Herpes Virus 8, Ebola, Hepatitis C virus	[208-212]
67	Favipiravir (avigan)	Guanine analogue, enters in infected cells and transformed into flavipiravir ribofuranosyl phosphate, inhibit RNA dependent RNA polymerase.	SARS-CoV 2, Favipiravir treated patient's Fever and cough relief time reduced	Treatment against avian influenza, Ebola and norovirus	[213-215,104]
68	Tetra-O-galloyl beta-D-glucose	Inhibit SARS-CoV infection.	SARS-CoV	Not Known	[216]
69	luteolin	Inhibit SARS-CoV infection.	SARS-CoV	Not Known	[216]
70	S230 antibody from memory B	S230's Fab region binds and neutralizes	SARS-CoV	Not Known	[217]

	cell of SARS-CoV infected individuals	the SARS-CoV			
71	Monoclonal antibody m396 (from b cell of CoV infected person)	competitive role for RBD (of S protein) binding	SARS-CoV	Not Known	[50]
72	80R and CR301 (spike specific Monoclonal antibody)	Block the S-ACE-2 interactions and neutralizes the SARS-CoV	SARS-CoV	Not Known	[50]
73	Vaccinated with SARS-n DNA	T-cell immune response, cytotoxic T cell response against SARS DNA transfected alveolar epithelial cells.	SARS-CoV	Not Known	[218]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
74	Mice vaccinated with SARS-M DNA	T-cell immune response, cytotoxic T cell response against SARS DNA transfected alveolar epithelial cells.	SARS-CoV	Not Known	[218]

Table 5: Supporting drugs that helped to reduce the symptoms of patients of COVID-19.

Supporting drugs for COVID-19 treatment					
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
1	Azithromycin + Hydroxychloroquine	Interfering with bacterial protein synthesis,	SARS-CoV-2	Treatment against severe respiratory tract infection, skin infection,	[219,220]
2	Cortecosteroids (Methyleprednisolone)	May improve dysregulated immune response	Death rate of COVID-19 patient is reduced.Treated with Methyle prednisolone exhibit improved clinical symptoms compared to patient without methyleprednisolone.	Pulmonary and systemic inflammation in pneumonia	[221-225]
3	Ascorbic acid	Positive effect on maturation of T lymphocytes and NK (natural killer) cells,The oxygenation index was improved	Applied to CoV patient in China and recovered	Effective against Influenza virus, improves the immune health	[226-229]
4	Nitric Oxide + Epoprostenol	Effective against SARS-CoV-2	SARS-CoV-2	Common pulmonary	[230-233]

				vasodialator	
5	Sirolimus (Rapamycin)	It affect PI3K/AKT/mTOR pathway and inhibit	MERS-CoV	Immunosuppressant, mTOR kinase inhibitor	[151]
6	Tocilizumab (Actemra)	Antiviral activity	20 out of 21 patient in China recovered treated with Tocilizumab, about 500 patient have been treated.	Treatment of RA (Rheumatoid Arthritis) and systemic juvenile idiopathic arthritis	[234,235]
7	Sarilumab	Antiviral activity	More than 400 COVID-19 patients have been enrolled and targeted to treat with Sarilumab.	Treatment of RA (Rheumatoid Arthritis)	[236]
8	Anakinra	Antiviral activity	In Belgium 342 patient enrolled(for randomized trial) and 20 patient enrolled from Greece(non-randomized trial) to treat COVID-19	Used to treat RA patient	[237,238]
Sl No.	**Compound name**	**Targets of Drugs**	**Target CoVs**	**Other targets**	**References**
9	Ibuprofen	Promising therapeutic agent against COVID-19	SARS-CoV-2	Activators of ACE2 receptors	[239]
10	Thiazolidinediones	Potential upregulate the ACE2 receptor	No clinical evidence that it works against coronavirus	Type 2 Diabates mellitus drugs exhibit effective against H1N1, or Respiratory Syncytial Virus	[240]
11	Indomethacin (NSAID)	Blocks viral RNA synthesis,	SARS-CoV-2	Inhibit Canine Corona virus	[241]
12	Colchicine	Reduce inflammation in cardiac myocytes	COVID-19	Anti-inflammatory medicine for gut management,	[242,243]
13	Niclosamide and Ivermectin	Replication inhibitor	SARS-CoV	Anthelmintic drug,Ivermectin is potential inhibitor of viral RNA replication of dengue, Flavivirus, and Influenza, Inhibit interaction	[244-248]

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				between Integrase of HIV-1 virus and its nuclear transport receptor Importins	

Table 6: Traditinal medicines utilized world wide aginst COVID-19

Sl. No.	Herbal medicine/plants	Probable point of action	country	References
1	*Astragalus membranaceus*	Immunosuppressive	China	[249]
2	*Glycyrrhiza uralensis*	Immunosuppressive	China	[249]
3	*Saposhnikoviae divaricata*	Immunosuppressive	China	[249]
4	*Rhizoma Atractylodis Macrocephalae*	Immunosuppressive	China	[249]
5	*Lonicerae Japonica Flos*	Immunosuppressive	China	[249]
6	*Fructus forsythia*	Immunosuppressive	China	[249]
7	*Atractylodis rhizoma*	Immunosuppressive	China	[249]
8	*Radix platycodonis*	Immunosuppressive	China	[249]
9	*Agastache rugosa*	Immunosuppressive	China	[249]
10	*Cyrtomium fortunei J. Sm*	Immunosuppressive	China	[249]
11	Shen Fu Injection	Inhibition of by reducing the level of TNF-α, IL-1β, IL-6,IL-8, IL-10	China	[250-253]
12	Re Du Ning Injection	Inhibition of by reducing the level of TNF-α, IL-1β, IL-6,IL-8, IL-10	China	[250-253]
13	Qingfei Paidu decoction	Inhibit cytokine action related pathway	China	[254]
14	Lianhuaqingwen formula	Inhibited SARS-CoV-2 replication, reduce the pro-inflammatory cytokines	China	[255]
Sl. No.	**Herbal medicine/plants**	**Probable point of action**	**country**	**References**
15	Sangju Yin	Clear lung heat, expel phlegm,relieve cough, regulate patient's lung	China	[256]
16	Yinqiao San	Antiviral and antibacterial function	China	[256]
17	Shufeng Jeidu capsule with Arbidol	Effective against COVID pneumonia	China	[257]

VIII. CONCLUSION

This pandemic is causing severe public health crisis with huge food and nutritional shortage for underprivileged group of people (e.g. daily labour, construction workers, small farmers and small businessman) of third world countries like India, Nepal, Srilanka and Pakistan due to great lockdown. Due to high transmission rate, this disease demands special attention of healthcare support system to prevent, control and treatment of the patients of COVID-19. Many countries are at the threshold of "Community transmission". The future clinical research on SARS-CoV-2 may develop vaccines or potential drugs and therapeutics which will make our planet liveable.

Compliance with Ethical standards

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