REVIEW ARTICLE

Potential Pharmacological Options Against the Coronavirus

Muhammad Ijaz[1,2*] |Fawad Ahmed[3]| Jawad Ahmed[4]| Ghulam Murtaza[5]| Muhammad Ihtisham Umer[5] | Waseem Hassan[5]

[1]The Faculty of Medicine, Qilu Institute of Technology Jinan, China.

[2] Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, China.

[3]Department of Pediatrics, Mayo Hospital, King Edward Medical University, Lahore Pakistan.

[4]Gujranwala Medical College, Gujranwala, Pakistan

[5]Department of Pharmacy, COMSATS University Islamabad, Lahore campus, Lahore

ABSTRACT:

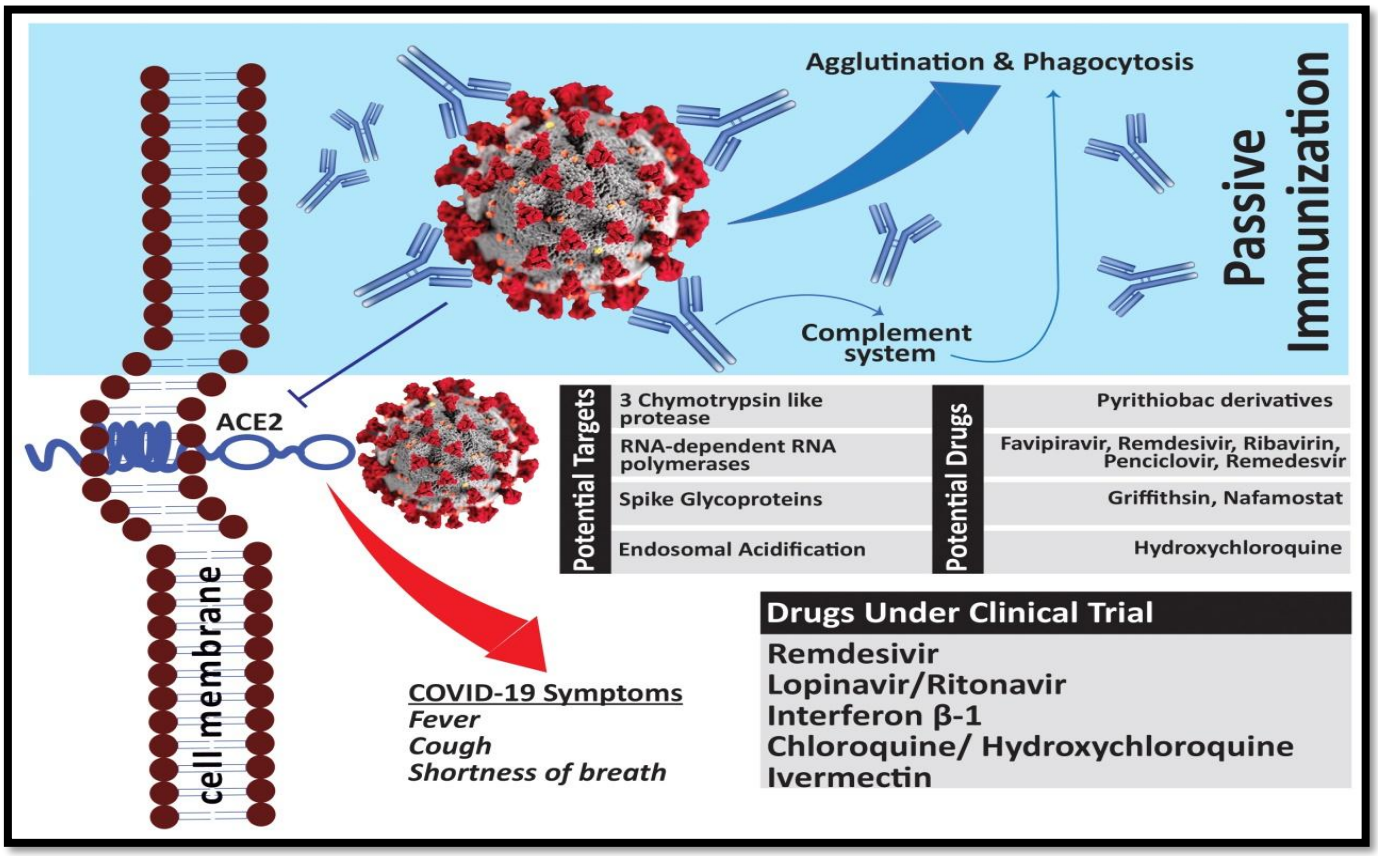
Background: The emergence of the novel coronavirus (2019-nCoV) and the resulting COVID-19 disease initiated a global pandemic, threatening human lives and societies on an unprecedented scale. While three previous coronavirus epidemics have been documented, the 2019 outbreak distinguished itself through its rapid global spread and multifaceted transmission pathways, swiftly escalating into a worldwide health emergency. **Objective:** This study aimed to analyze previous coronavirus epidemics by comparing their outcomes with the recent COVID-19 pandemic. A further objective was to discuss pharmacological agents demonstrating potential in-vitro and in-vivo activity against the virus, with a critical focus on the evidence for remdesivir and chloroquine. **Methods:** A comparative analysis was conducted, evaluating the epidemiological trajectories and outcomes of previous coronavirus outbreaks against the COVID-19 pandemic. Additionally, a review of scientific literature was performed to identify and assess pharmacological agents with reported anti-COVID-19 activity in both laboratory and animal studies. **Main Outcome Measures:** The primary outcomes were the comparative transmissibility and scale of the COVID-19 pandemic relative to previous coronavirus epidemics, and the summarized preclinical evidence for the efficacy of selected pharmacological agents. **Results:** The analysis confirmed that the COVID-19 pandemic spread more rapidly and extensively than previous coronavirus epidemics. The review identified several agents with promising in-vitro and in-vivo activity. However, the capacity of remdesivir and chloroquine for treatment and prevention remains a subject of intense debate, underpinned by premature findings, a lack of robust clinical trials, and significant concerns regarding long-term safety. **Conclusion:** The COVID-19 pandemic represents a significant escalation in the threat posed by coronaviruses. While certain drugs show preclinical promise, the evidence for their clinical application, particularly for chloroquine and remdesivir, is insufficient and often conflicting. This underscores the critical and urgent need for large-scale, rigorous clinical trials to establish safe and effective therapeutic protocols.

Key words: COVID-19; SARS-CoV; MERS-CoV; pandemic

***Corresponding author**

Muhammad Ijaz
Department of Pharmacology, School of Pharmaceutical Science, Shandong University, Jinan, China.
email:drmuhammadijaz1@gmail.com

Graphical Abstract



1. Introduction

Since December 2019, numerous instances of a pneumonia-like condition have reported in the central Chinese city of Wuhan. Chinese health specialists investigated the causative agent that is a novel coronavirus (nCoV-19) [1]. A confederation of scientists, government agencies and research organisation identified six sequences of this nCov-19 and released on Global Initiative on Sharing All Influenza Data (GISAID). Genomic analysis signposted the similarity with severe acute respiratory syndrome related coronavirus (SARS-CoV) family. [2]. Since its initial outbreak, COVID-19 has grown into catastrophe overstretching to the limits of pandemic, killing thousands of people worldwide, playing havoc with world economy and pushing others to the limits. Whilst we write these lines, global population is facing enforced lockdown in their homes as reported infections toll reaching 0.48 million with approximately 22000 deaths.

Coronaviruses causes respiratory and intestinal infections in living things, including Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV [3]. SARS-CoV was first emerged in the Guangdong province, China, in 2002–2003 svictimising nearly 8,000 individuals in more than 30 nations and casualties associated with this endemic was nearly 800 patients. The previous strains of coronavirus (SARS and MERS–CoV) possibly be emanate from bats and attacked to humans [4].

Preliminary epidemiological investigations revealed that the on-going pneumonia-like cases in Wuhan city have been relating to a seafood and animal haberdashery, possibly this point is a zoonotic origin of the nCoV-19. [5]. The Wuhan Health Commission informed, "the likelihood of human-to-human transmission cannot be ruled out". Later it was confirmed as health-care workers were found infected [6]. Moreover, the people infected with the nCoV-19 should take apposite care to relieve and treat sign and indications, and those with Spartan sickness should receive optimised supportive care. Researchers still do not precisely denied the role of animals in transmitting nCoV-19 to humans, the chief suspicion is the pangolin. [7]. When SARS knockout Asia in 2002 and found triumph in several countries. The situation beheld very scary with a mortality rate of 10 percent. In fact no drug was appeared to be operative against nCoV-19. Owing to the strict health care practices including isolation, quarantine and contact tracing along with their appropriate compliance within few months SARS was brought under control, and spreading and transmission was ruled out for the most parts [8]. But the transformation noted in the current nCoV-19 and previous SARS outbreak was that former had more severe symptoms, that provoked the people to pursue instantaneous treatment and management in hospitals as compared to the COVID-19 patient [9].

2. Lessons from the past corona virus outbreaks

2.1. Severe Acute Respiratory Syndrome Coronavirus (SARS) epidemics:

SARS-CoV was defined very quickly subsequent to its advent in southern China back in 2002-03 [10]. This outbreak led to 774 death in 11 countries [11]. Consequently, SARS-CoV was present in palm civets cats [12]. Although, early hypothesis and assumptions about the zoonotic transmission of nCoV-19 was overturned by several observations. Firstly, SARS-CoV was only detected in civets from the bazaar, but not those in the wild [13]. Secondly, the virus possessed extraordinary potential of mutation, the virus was enduring prompt evolutionary gene modification in civets [14]. Thirdly, on comparison SARS-CoV 2003 vs SARS-CoV 2004 epidemic, the extensive studies have exhibited less efficient use of the human angiotensin converting enzyme 2 (ACE2) receptor [15] and confirmed resistance to antibody inhibition [16]. Lastly, whereas substantial quantity of antibody to SARS-CoV was identified in 80% of the civets from only one animal market however residual civets were confirmed absence of antibody in Guangzhou other markets and farms. [17].

A molecular surveillance study was carried out in several mammals in Hong Kong to pursuit the eventual source of this virus. Amongst the 127 bats (including 8 bat species), 20 monkeys and 60 rodents fathomed, SARS-CoV was only spotted in Rhinolophus sinicus, Rs (horseshoe bats) [18]. Subsequently, another research group uncovered the presence of SARS-CoV in Chinese horseshoe bats, greater horseshoe bats, and big-eared horseshoe bats in other provinces (Hubei and Guangxi)of China [19]. Since 2003 339 SARS-CoV genomes have been sequenced. Breakup of these genomes include 274, 18 and 47 genomes from human, civets and bats respectively [20].

2.2. Middle Eastern respiratory syndrome coronavirus (MERS) epidemics:

MERS was first identified in 2012 caused by coronavirus possessed the symptoms of viral respiratory disease of humans. The WHO numerate 2,279 confirmed cases between 2012 and December 2018 unfortunately counting 806 allied deaths globally [21]. Even though victims had been reported from 27 countries, the majority of cases (1,901) were from Kingdom of Saudi Arabia. Couple of cases were also reported in the America, both of whom were health care workers those acquired infection

from Kingdom of Saudi Arabia [22]. It was not reported elsewhere. MERS-CoV is also a zoonotic disease, dromedary camels are the intermediate hosts and humans are the terminal host for MERS-CoV, [23] Similarly, bats are probable the foremost mammalian cause of MERS . MERS infection characterized by asymptomatic or mild respiratory symptoms to severe acute respiratory disease and death. Threat factors include elder age, co-morbidities and immunosuppression [24, 25]. Currently, no vaccine and drug has been approved for the treatment, only symptomatic treatment is being practiced worldwide. Transmission of MERS was associated to personal touch most expected owing to droplet transmission [26].

Infection stoppage policies were formulated and being practiced whole heartedly by the hospitals and clinics during the MERS outbreak [27] Certain very successful policies were practiced by the south korea amid MERS outbreak and found to be very successful. [28]. Resultantly, >20% of cases was reported [29]. Widespread environmental adulteration has been documented in clinical areas and housing MERS patients [30]

3. Recent Coronavirus (COVID-19) pandemic:

The third zoonotic human coronavirus of the century emerged in end of 2019. Symptoms of nCoVID including pyrexia, dyspnoea, and bilateral lung infiltration in the utmost austere conditions [31]. After widespread conjecture about a causative agent, the Chinese CDC confirmed a novel virus on 9th of January 2020 [32]. The nCoV19 was extracted from a patient and successively confirmed in 16 further patients [33]. While nCoV19 was rapidly prejudiced as the possible causative agent.

The first genomic sequence of nCoV19 was posted on 10th of January very next day after its endorsement, by Dr. Yong-Zhen Zhang from Fudan University, Shanghai [34]. Successively, five additional nCoV19 genome were submitted to the GSAID database on 11th January. This allowed scientist all over the world to begin investigating and analysing the nCoV19. On 17th January, there were 62 confirmed incidents in China. Moreover, three exported infected travellers were identifying in Thailand and Japan. The sequences of these exported cases have also been submitted on the GSAID database. [35].

Most of these mortalities accompanying with COVID-19 infection had substantial co-morbidities and were elder in age (>50) Similar to the MERS-CoV. Symptoms are also similar to the SARS and MERS -CoV. Related to SARS-CoV (10% mortality) and MERS-CoV (35% mortality), the nCoV19 appears to be less contagious at this point with the exclusion of the elderly and those with Comorbidities. [36]. By the end of March, 2020 this virus has been spread to over 165 countries and have affected 471,282 people. About 21,297 casualties has been reported.

A pulmonary protein Angiotensin-converting enzyme 2 (ACE2) is expressed in epithelial cells of the alveoli. This receptor is considered as a receptor target for SARS-CoV, that plays a dynamic role in pulmonary injury caused by the virus [37] Pulmonary damage caused by this viron is related to both ACE2 and components of renin-angiotensin system. Pulmonary damage is encouraged by SARS-CoV. *In-vivo* and *in-vitro* studies established that ACE2 expression was down regulated after the coronavirus infection [38]. Thus, ACE2 may have duple properties on SARS-CoV [39] as firstly, it proved to be a receptor for the infection of SARS-CoV, and then its consequential recepror down regulation encourages lung injury. [40] The extensive research is required to understand and establish the role of ACE 2 in the pathogenesis of nCoV-19 and associated pulmonary injury. Therefore, advanced research is prerequisite to scrutinise the expression of ACE 2 in COVID-19 patients as this can prove to be an important drug target. The extensive studies can be conducted to investigate the potential of role of ACE 2 Agonist to

prevent the pulmonary symptoms of these viral strains. Previous outbreaks of coronavirus like family share close resemblance with COVID-19 in signs and symptoms but mortalities rates differ markedly. The lower mortality percentage of COVID-19 as compared to SARS-CoV and MERS may be misleading phenomenon because of the pandemic nature of the former. However the percentage of morbidities and impact of COVID-19 surpasses previous similar outbreaks, meaning that it is becoming more contagious with the passage of time. The involvement of ACE2 in SARS-CoV provides an interesting drug target that require a future attention.

3.1. Genome

The first coronavirus genome was discovered nearly thirty years ago, due to the non clinical effects in human its studies were terminated. RNA viruses had unique discriminatory packaging of its genomes in a various arrays, mostly equipped with genomic packaging signals. Lately a study suggested that selective coronavirus genome packaging is critical for in vivo evasion of the host innate immune response [41]. Selective amalgamation of the coronavirus genome into virions is arbitrated by a cis-acting RNA packaging signal. Packaging signals fluctuate amid these and novel coronavirus strains. These packaging signals either recognised by nucleocapsid or the membrane protein. This unique characteristic makes the uniqueness of the novel corona virus. Henceforth, unique camouflaged genome packaging helps for the circumvention of host innate immunity [42].

3.2. Characteristics of nCoV19

nCoV19 is an enveloped, single-stranded RNA beta-coronavirus. Like SARS and MERS-CoV, the nCoV19 genome encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins. The four non-structural proteins highlighted earlier are important enzymes in the viral life cycle. These proteins were predicted as attractive drug targets to develop antiviral drugs against SARS and MERS- CoV [43].

Initial studies revealed the genomic sequences of nCoV19 specified that the catalytic sites of the four nCoV19 enzymes, and has a extensive sequence resemblance with the compatible to SARS and MERS-CoV enzymes. It was also revealed that potential drug binding sites is virus are conserved across nCoV19, SARS and MERS [44]. It is plausible to argue to consider re-using of existing MERS and SARS inhibitors for nCoV19 [45].

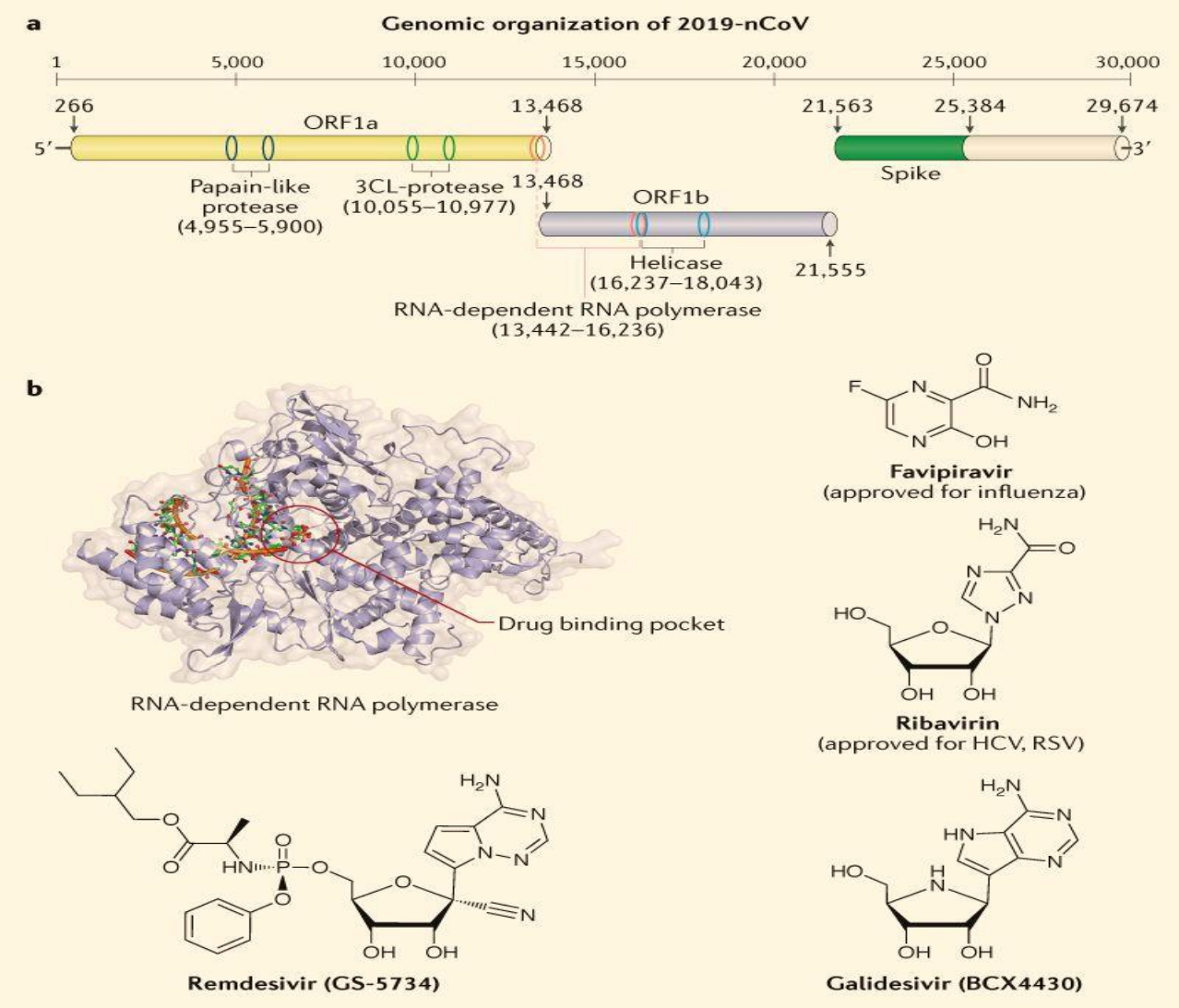


Fig. 1: Potential **drug targets for beta-coronaviruses**. **a. shows the** nCoV19 genome (MN908947.3), **b**. highlights the drug binding pocket in the RNA-dependent RNA polymerase of SARS (PDB: 6NUR, 3H5Y). Chemical structures of potential compounds are also provided. Figure is adopted from (https://pymol.org).

3.3. Super spreading of nCoV19 *vs* SARS *vs* MERS

Super spreading is the augmented and uncontrolled transmission of a virus. Both SARS and MERS outbreaks had familiar evidence of super spreading among the patients [25]. In general, both epidemic corona virus maintain a low rate, the rate spread from an individual infected patient. In the previous outbreaks 10% of SARS and MERS patients have been related to super spreading i.e. causes super spreading [46]. Previously it was belived that nCoV19 contact causes some degree of human to human spread. However, incremental alleviation in new cases shows the existence of super-spreading in this particular viral strain. Strong evidence exists that, like previous outbreaks super spreading could occur from the zoonotic source. The leeway of super spreading may endure a role in this current nCoV19 outbreak.

In the early part of the outbreak, the absence nosocomial infections. In the two prior corona vitus epidemics, nosocomial infections were reported. The current reports of frequent diseased health care workers in indicates human to human infection can occur with nCoV19 and this is the reason of super spreading of the disease [47]. Super spreading in COVID-19 and has a potential to make the outbreak even more difficult to control [48]. Previous outbreaks were endemic however owing to rapid super spreading the spread of nCoV-19 is currently pandemic.

4. Passive Immunization

Passive immunization is a natural defense mechanism. The immune systems will have to produce antibodies against the foreign particles, the helped the living organisms to recognize and fight a repeat attack by the coronavirus. But while we wait for a vaccine to prevent infection, those antibodies could be used to help infected people. Antibodies can be extracted from the blood serum of surviving patients, and then injected into infected people. Those people should then develop a "passive immunity." A passive immunization is a treatment for infected patients, but it doesn't provide long-term protection. It's called passive immunization, because the recipient body hasn't actively produced any antibodies itself. And as a result, the antibodies it "borrows" will provide protection or help to fight an infection, but only for a short period of time. Passive immunization usually lasts for a few weeks or months, after which those borrowed or the host body breaks down donated antibodies, within about 30 days. The patient can shall be at risk of infection by the same pathogen, because their own immune system has not been stimulated to produce its own, more permanent antibodies. Patients who are surviving a COVID-19 infection with passive immunization would still be at risk of re-infection, unlike patients who had been infected and fought off the disease with their own immune system actively producing the antibodies.

Passive immunization was first introduced by Emil von Behring, a German immunologist and serologist, in 1890. He developed it for diphtheria, a highly infectious, bacterial disease, responsible for the death of thousands of children back then. Emil von Behring was awarded the first Nobel Prize for medicine in 1901. For his successes in the development of blood serum-derived medicines against diphtheria and tetanus, von Behring was hailed by the press as the "saviour of children" and during World War I as the "saviour of soldiers."

Serum therapy was also used in 2014 at the outbreak of the Ebola epidemic in West Africa. Four years later, during another outbreak of Ebola in the Democratic Republic of Congo, a drug consisting of antibodies was used to treat patients and prevented

the virus from spreading in the body. That's said to have reduced the mortality rate by 30 percent. Researchers now want to use antibodies extracted from the blood serum of recovered coronavirus patients to offer a passive immunization against the new disease. And the work has begun. In February, a special clinic for serum therapy was established in Shanghai, China. At large scale the pharmaceutical companies that has the capacity to develop the antibodies at large scale should come forward and plan to obtain an antibody mixture called from the blood plasma of recovered coronavirus patients and use it to develop a new drug. The drug should consist of various purified antibodies that can fight against the nCoV-19. That means that researchers do not have to spend time and effort identifying the antibodies needed to fight diseases, such as the new coronavirus. Scientist can also test whether antibodies obtained in 2003 from the blood serum of former SARS patients can neutralize COVID-19 patient. Erstwhile explained the genomic similarities between SARS and COVID-19 and both causes severe acute respiratory syndromes, so there could be useful similarities in the antibodies.

While drugs to treat patients with COVID-19, and vaccines to prevent infection are being developed, a fast-acting, stopgap serum therapy could be useful as a first aid for high-risk patients. High risks groups include older people, around the ages of 70 or 80, and people with existing, serious conditions, and that may also include younger people. It is believed that if the antibody containing drug is developed, it is very easy to supply it large number of potential patients quickly, because it can be produced rapidly in huge cell tanks. But it will take a vaccine to slow and eventually stop the transmission of this new coronavirus, and labs around the world are currently working on that at full speed.

5. Pharmacological agents attempted in covid-19 pandemic:

Food and Drug Administration (FDA) has approved nucleoside analogues (favipiravir and ribavirin) and investigational nucleoside analogues (remdesivir and galidesivir) may have probable activity against nCoV19. They target the RNA-dependent RNA polymerase enzyme and block viral RNA synthesis in RNA viruses. Numerous drugs, like ribavirin, interferon, lopinavir-ritonavir, and corticosteroids have been used in patients with SARS / MERS- CoV [45].

Favipiravir a guanine analogue approved for influenza treatment, can effectively inhibit the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus, and a recent study reported its activity against nCoV19 (EC_{50} = 61.88 μM in Vero E6 cells). [49]. Patients with nCoV19 are being recruited in randomized trials to evaluate the efficacy of favipiravir. Ribavirin is a guanine derivative approved for treating HCV and respiratory syncytial virus that has been evaluated in patients with SARS and MERS-CoV, Remdesivir is a phosphoramidate prodrug of an adenine derivative an approved HIV reverse transcriptase inhibitor. Remdesivir reported to active against RNA viruses including MERS and SARS-CoV in cell cultures and animal models. Recent studies has proved that remdesivir inhibited nCoV19 (EC_{50} = 0.77 μM in Vero E6 cells). Earlier this year nCoV19 patient in america recuperated after the IV administration of remdesivir. Currently two phase III trials are undergoing since February of this year to evaluate IV remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) in patients with nCoV19, that will accomplished in April 2020 [50]. Galidesivir an adenosine analogue that was initially approved for HCV, this has also antiviral potential in pre-clinical studies against numerous RNA viruses, such as SARS and MERS- CoV [43].

Approved protease inhibitors including disulfiram, lopinavir and ritonavir has been approved for HIV-1 protease, also bearing the killing potential against SARS and MERS- CoV (Table 1), but clinical relevance is to be established [43]. Yet, it is controversial whether protease inhibitors could efficiently and successfully inhibit the 3-chymotrypsin-like and papain-like proteases of nCoV19. The spike glycoprotein is also a promising target [43]. These compounds also got the ability to kill several viruses

Pegylated interferon alfa-2a and -2b, has been permitted for the treatment of HBV and HCV, possibly to stimulate innate antiviral responses in patients infected with nCoV19. However, it is uncertain whether a pegylated interferon and a nucleoside compound could act synergistically against nCoV19.

Small-molecule agents approved for other human diseases may modulate the virus–host interactions of nCoV19. An approved immune modulator, chloroquine, shows inhibitory effects against nCoV19 (EC_{50} = 1.13 μM in Vero E6 cells) [49]. Chloroquine an antimalarial drug famously used for the treatment of malaria, chemically it is a weak base that increases the intracellular pH which normally work under acidic environment. This hinders the virus capacity in a dual manner. Firstly it affects the ability of virus to penetrate the cells; secondly it restricts the replication of virus inside cells. Philippe Gautret *et al.* reported in March 2020 that hydroxychloroquine is effective in reducing the virus load or even clearance from the human body and azithromycin has a synergistic effect [51].

Nitazoxanide, approved for diarrhea treatment, could also inhibit nCoV19 (EC_{50} = 2.12 μM in Vero E6 cells). The antiviral efficacy of such agents needs to be assessed in clinical studies [45].

Recently Ivermectin is anthelmintics has also showed virus killing potential *in-vitro* by inhibiting cytosolic importin (IMP α/β1) heterodiameric complex mediated nuclear import of viral proteins [52].

Clinical trials are considered as the undisputed standards for the development of drugs and utilization of these drugs in the human. These trials last for months or years and conducted on thousands of patients and healthy volunteers, frequently worldwide patients are included in the trials. Volunteers are allocated randomly to either receive the drug under investigation or a placebo, usually these studies are conducted double blindly to further reduce bias.

Table:1 Potential drugs against the coronavirus is enlisted in the table.

Infectious disease	Drug Targets	Anti-viral agents	Reported mechanism of action
Virus-based treatment strategies			
nCoV19; Influenza	RdRp	Favipiravir	Inhibits RdRp
nCoV19, MERS-CoV, SARS-CoV, RSV, HCV	RdRp	Ribavirin	Inhibits viral RNA synthesis and mRNA capping
nCoV19	RdRp	Penciclovir	Inhibit RdRp

nCoV19, MERS-CoV, SARS-CoV	RdRp	Remedesvir	Terminates the non-obligate Chain
MERS-CoV, SARS-CoV	PLpro	Disulfiram	Inhibits PLpro
MERS-CoV	PLpro	Compound 6	Inhibits PLpro
SARS-CoV	3CLpro	Pyrithiobac derivatives (6-5)	Inhibits SARS-CoV 3CLpro
SARS-CoV, MERS-CoV	3CLpro	Neuraminidase inhibitor analogues (compound 3k)	Inhibits 3CLpro
SARS-CoV, MERS-CoV, MHV	Helicase	SSYA10-001 and ADKs	Inhibits helicase without affecting ATPase activity
nCoV19, MERS-CoV	Spike glycoprotein	Nafamostat	Inhibits spike-mediated membrane fusion
SARS-CoV	Spike glycoprotein	Griffithsin	Griffithsin binds to the SARSCoV spike glycoprotein, thus inhibiting viral entry
MERS-CoV	Spike Glycoprotein	MERS-5HB	Inhibits pseudo typed MERSCoV entry and S proteinmediated syncytial formation
MERS-CoV	Spike	Dihydrotanshinone	Blocks the endosomal entry

	glycoprotein	E-64-C, and E-64-D	Pathway
Host-based treatment strategies			
nCoV19; SARS-CoV; MERS-CoV	Interferon response	Recombinant interferons (interferon-a , interferon-	Exogenous interferons
nCoV19 SARS-CoV MERS-CoV	Endosomal acidification	Chloroquine	A lysosomatropic base that appears to disrupt intracellular trafficking and viral fusion events
Broad-spectrum (e.g. coronaviruses, nCoV19)	Interferon Response	Nitazoxanide	Induces the host innate immune response to produce interferons (a and b) by the host's fibroblasts and protein kinase R (PKR) activation
SARS-CoV, MERS-CoV, HIV, HCV	Cyclophilins	Cyclosporine A	Cyclophilin inhibitor that could modulate the interaction of cyclophilins with SARS-CoV nsp1 and the calcineurin–NFAT pathway
MERS-CoV	Kinase signaling	Rapamycin	Inhibits the ERK/MAPK and PI3K/AKT/mTOR pathways

	pathways		significantly inhibited MERSCoV replication
MERS-CoV SARS-CoV	Abelson Kinase	Imatinib mesylate	Blocks events of early viral entry and/or post-entry

Abbreviations

3CLpro: 3C-like protease, HBV: hepatitis B virus, HCoV: human coronavirus, HCV: hepatitis C virus, IAV: influenza A virus, MERS: Middle East respiratory syndrome, MERS-CoV: Middle East respiratory syndrome coronavirus,, PLpro: papain-like protease, RdRp: RNA-dependent RNA polymerase, RSV: respiratory syncytial virus, SARS-CoV: severe acute respiratory syndrome coronavirus,

Conclusion:

COVID-19 pandemic is wreaking havoc in an unprecedented manner around the globe. The lessons from the erstwhile coronavirus outbreaks suggests similarities in transmission and symptoms but patterns of severity and contagiousness have seen modifications which require urgent attention of scientific community. ACE2 has been found to be involved in SARS-CoV and it is worth examining as drug target. As most of the ACE inhibitors in markets are non-selective, it warrants an urgent precaution in patients with co-morbidities administered with ACE inhibitors during this pandemic. Pharmacological evidences suggest encouraging results of various anti-viral drugs as scientific community races to find solution amidst pan[51]demic. The absence of long-term clinical trial and under-established safety profile is presenting a challenge in this situation that can be taken up as preparation for next such epidemic.

Conflict of Interest: It is declared that there is no conflict of interest among any of the author.

Contribution of authors:

H.A and W.H design the study, J.A and F.A collected the Data, G.M helped in writing and data analysis.

Ethical Statement: The study was approved by the Institutional Ethical Review Committee (IREC) of The University of Lahore.

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