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POTENTIAL DRUG CANDIDATES FOR TREATMENT OF COVID-19

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ABSTRACT: The late December of 2019 witnessed an outbreak of viral pneumonia of unknown etiology (VPUE) in the Wuhan city of Hubei province, China. Later it was identified as a novel strain of β-genus Coronavirus, which is similar to the Severe Acute Respiratory Syndrome (SARS) virus, which was a global pandemic during 2002-03. This novel coronavirus is rapidly spreading with an R0 of 2 and has an incubation period of 2-14 days. It spreads through human-to-human transmission and by fomites (articles and surfaces contaminated by affected persons). The World Health Organization acted immediately to prevent the spread of the virus by declaring it as a Public Health Emergency of International Concern (PHEIC). It has been declared as a pandemic, and several sets of guidelines have been issued by WHO, including social distancing norms and hygiene practices yet, this novel coronavirus continues to spread at an alarming rate leading to many fatalities across the globe. Since this novel coronavirus shares similar characteristics with other coronaviruses, some of the known treatment options can be reused in the treatment of this novel coronavirus. As of now, no vaccine has been approved for the prevention of this rapidly spreading novel coronavirus. Hence, the management of affected persons with the available treatment options becomes indispensable. This article briefs about the treatment options available, which include antiviral drugs like Remdesivir, Ribavarin, anti-retroviral drugs like Lopinavir and Ritonavir, antimalarial drugs like Chloroquine and Hydroxychloroquine, Tocilizumab, Ivermectin, and also traditional medicine.

INTRODUCTION: Coronaviruses (CoVs) are the largest viruses belonging to the order Nidovirales, which includes Coronaviridae, Arteriviridae, and Roniviridae families. The Coronaviridae has two sub-families, namely Coronavirinae and Torovirinae. Serologically, the Coronavirinae sub-family is categorized into four groups, namely Alpha (α-coronaviruses), Beta (β-coronaviruses), Gamma (γ-coronaviruses), and Delta (δ- coronaviruses).

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Out of these, the alpha and beta coronaviruses are found to infect the mammals, and the gamma and delta coronaviruses are found to infect the birds. The genome of the coronavirus (CoV) is enveloped, positive single-stranded RNA whose size varies between 26-32 Kb (kilobases). The organization of the coronavirus genome is 5′-leader-UTR- replicase-S (Spike)–E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTR-poly (A) scattered within the structural genes at the 3′ end of the genome. Till date, there are six known coronaviruses that are thought only to cause mild, self-limiting respiratory infections in humans prior to the SARS outbreak in 2002-03 [1].

Generally, human coronaviruses account for nearly 15-30% of common cold infections worldwide but

occasionally leads to lower respiratory tract infections. The six known human coronaviruses comprise of two alpha coronaviruses (HCoV229E, HCoV-NL63) and four beta corona-viruses (HCoV-OC43, HCoV-HKU1, HKU4, HKU5). The respiratory ailments caused due to these coronaviruses are severe in neonates, elderly, and persons with underlying illness. It has been suggested that these human coronaviruses may play a role in the development of multiple sclerosis. However, there is no evidence till date to support this.

SARS Cov, belonging to 2b β-coronaviruses, is responsible for the severe acute respiratory syndrome outbreak during 2002- 03 in the Guangdong province of China. During the SARS outbreak, 8098 cases and 774 deaths have been reported, with a mortality rate of 9%. This respiratory tract infection has been reported more in persons of age above 60 yrs. The source of this coronavirus was traced to Chinese horseshoe bats because the studies on both bat coronavirus and SARS CoV Suggested that these both use the same ACE2 receptor. However, the SARS-CoV spreads only with direct contact with infected people; the outbreak has been contained within a year. SARS-CoV infects the epithelial cells within the lungs and induces more pro-inflammatory cytokines, which lead to cytokine storm and cause lung injury. In most cases patients die due to the acute respiratory distress syndrome caused due to lung damage.

After the SARS outbreak, a novel coronavirus emerged in the Middle East countries during 2012 causing severe respiratory infections, and it is named as Middle Eastern Respiratory Syndrome (MERS). MERS was caused due to 2c β-coronaviruses HKU4 and HKU5, which originated from bats and infects humans through intermediate hosts such as camels. As of 2013, 855 cases and 333 deaths have been reported due to MERS-CoV infections. Unlike SARS, MERS CoV uses DPP4 (dipeptidyl peptidase 4) as its receptor [1, 2].

After these coronavirus outbreaks, late December of 2019 witnessed a novel coronavirus outbreak, *i.e.*, SARS-CoV2. It is said so because the genome of SARS CoV is 70% similar to this nCoV. Hence, its source is traced to bats. But researches show that the nCoV used pangolins as an intermediate host to infect humans. This nCoV is rapidly spreading and already spread over 190 countries. Unfortunately, there is no vaccine and appropriate drugs available for the treatment of this COVID-19 till date. As it shows more similarity to SARS-CoV, the drugs used to treat SARS can be screened for treating COVID-19. In this article, we will see about the potential drug candidates that can be involved in clinical trials to prove the efficacy of treating covid-19 and to know about the side effects caused due to the drugs.

Structure of SARS-CoV2: The SARS-CoV2 genome (30 kb in size) encodes a large non-structural polyprotein, open reading frame (ORF) 1ab, which is further proteolytically cleaved to generate 15/16 proteins, four structural proteins and five accessory proteins (ORF3a, ORF6, ORF7, ORF8, and ORF9). The four structural proteins consist of the spike surface glycoprotein (S), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N), which are essential for SARS-CoV2 assembly and infection[3].

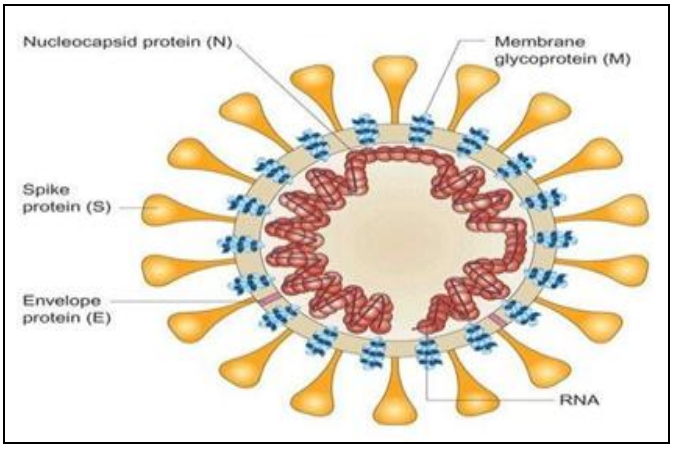

FIG. 1: STRUCTURE OF CORONAVIRUS
(Source: From severe acute respiratory syndrome 4)

The S protein (~150 kDa), utilizes an N-terminal signal sequence and is N-linked glycosylated. Homotrimers of the virus-encoded S protein make up the spike structure on the surface of the virus. The trimeric S glycoprotein is a class I fusion proteins attached to the host receptor. The M protein is the most abundant structural protein in the virion. It is a small (~25–30 kDa) protein with 3 transmembrane domains and is thought to give the virion its shape. It has a smaller N-terminal glycosylated ectodomain and a much larger C-terminal endodomain, which extends 6–8 nm into

the viral particle. The E protein (~8–12 kDa) is found in small quantities within the virion. E proteins from coronaviruses are highly divergent but have a common architecture. The membrane topology of E protein is not completely resolved, but most data suggested that it is a transmembrane protein. The E protein has an N-terminal ectodomain and a C-terminal endodomain and has ion channel activity.

The N protein constitutes the protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD). These domains bind with RNA *in-vitro*, but each domain uses different mechanisms to bind RNA. A fifth structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coronaviruses. The protein acts as a hemagglutinin, binds sialic acids on surface glycoproteins, and contains acetyl-esterase activity. Therefore, understanding the structure and function of the spike protein can help develop monoclonal antibody drugs and guide the design and development of vaccines [1, 5].

Pathogenesis of SARS-CoV2:

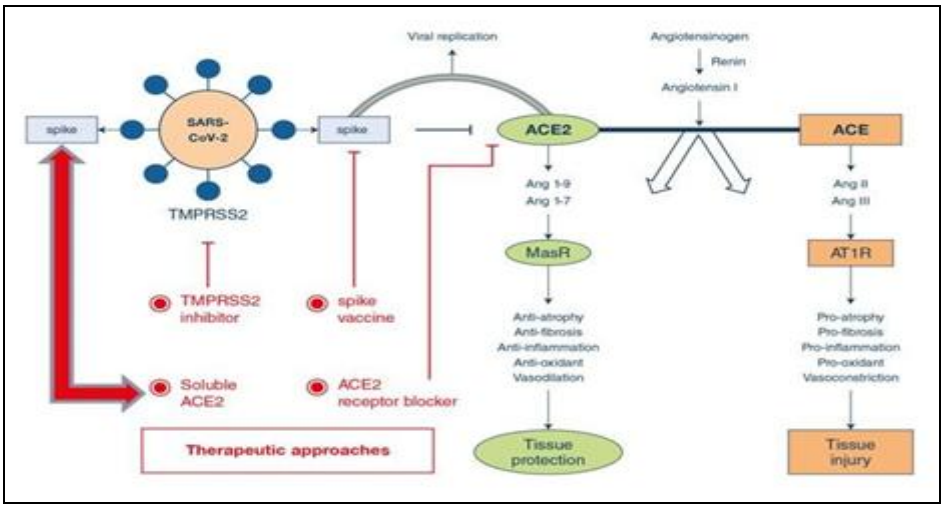

FIG. 2: SOURCE: FROM ANGIOTENSIN-CONVERTING ANANGIOTENSIN-CONVERTING ENZYME 2 (ACE2) AS A SARSCoV2 RECEPTOR: MOLECULAR MECHANISMS AND POTENTIAL THERAPEUTIC TARGET [6]

All known human coronaviruses are known to cause upper respiratory tract infections, whereas the SARS-CoV and MERS-CoV are capable of causing atypical pneumonia. This is because of binding with host receptors like ACE2 and DPP4. Since the nCoV mostly resembles the SARS-CoV, we can conclude that it also binds to the ACE2 receptor and specifically binding to the ACE2 receptor, it could trigger an increase of pro-inflammatory cytokines such as interferons, interleukins, chemokines, *etc*.

The interferons (IFNs) are a family of cytokines that play a central role in innate immunity to viruses and other microbial pathogens. They are classified into three major types (types I, II, and III) on the basis of their receptor specificity. Interferon-stimulated genes encode protein products with antiviral, antiproliferative, or immunomodulatory properties. Such effects have led to the therapeutic use of IFNs (often in combination with other drugs) in the treatment of viral diseases such as hepatitis C and hepatitis B, certain types of leukemia and lymphoma, and multiple sclerosis. In contrast to the interferons, the interleukins are a diverse family of immune system regulators that function primarily in immune cell differentiation and activation. They may be either pro- or anti-inflammatory [7].

SARS-CoV2 spike binds to human ACE2 with approximately 10 to 20 fold higher affinities than the SARS-CoV spike, making it easier to spread from human-to-human. Upon entry into alveolar epithelial cells, SARS-CoV2 replicates rapidly and triggers a strong immune response, resulting in cytokine storm syndromes and pulmonary tissue damage. Cytokine storm syndromes, also known as hypercytokinemia, are a group of disorders

characterized by the uncontrolled production of pro-inflammatory cytokines and are important causes of Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure.

Analysis of the first 99 confirmed cases of SARS-CoV2 infection revealed that cytokine storm syndromes occurred in patients with severe COVID-19, and 17% had ARDS, and among them, 11% of patients deteriorated within a short period of time and died of multiple organ failure. In addition, the numbers of total T cells, CD4+ T and CD8+ T cells are decreased in patients with SARS-CoV2 infection and the surviving T cells are functionally exhausted, suggesting a decreased immune function in SARS-CoV2 infected patients. ARDS decreased immune function, and secondary infection further worsens respiratory failure [3].

Treatment of Covid-19: Till now, there is no promising cure for COVID-19 is assured. However, certain drugs either alone or in some combinations have shown improving the condition of COVID-19 patients. This includes anti-viral drugs, anti-malarial drugs, corticosteroids, monoclonal antibodies *etc*., and convalescent plasma therapy showed promising results in treating COVID-19 patients.

Chloroquine and Hydroxychloroquine: Chloroquine (CQ) is an amine acidotropic form of quinine and hydroxychloroquine (HCQ) differs from chloroquine by the presence of a hydroxyl group at the end of the side chain. The N-ethyl substituent is β-hydroxylated. For decades, CQ and HCQ are front-line medications for the treatment and prophylaxis of malaria and are also used to treat autoimmune diseases, including rheumatoid arthritis. Several clinical trials in China have shown chloroquine phosphate, an aminoquinoline used in malaria treatment, to be effective against COVID-19 at a dose of 500 mg/day.

Chloroquine phosphate also played a promising role in the management of the Zika virus and SARS-CoV outbreaks. Chloroquine acts by increasing the pH of intracellular vacuoles and altering protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational protein modification in the Golgi apparatus. In macrophages and other antigen-presenting cells, chloroquine interferes with antigen processing, thereby achieving an antirheumatic response. In addition, chloroquine alters the glycosylation of the cellular receptors of coronaviruses [8].

Hydroxychloroquine, a less toxic aminoquinoline, has an *N*-hydroxyethyl side chain in place of the *N*-diethyl group of chloroquine. This modification makes hydroxychloroquine more soluble than chloroquine. Similar to chloroquine, hydroxy-chloroquine increases the pH and confers antiviral effects. In addition, hydroxychloroquine has a modulating effect on activated immune cells, down-regulates the expression of Toll-like receptors (TLRs), and TLR-mediated signal transduction and decreases the production of interleukin-6.

Hydroxychloroquine shows a high partitioning in tissue, including lung and brain. This chemical property offers a key clinical advantage in the case of COVID-19. Since the structure and mechanism of action of chloroquine and hydroxychloroquine (HCQ) are exactly the same except an additional hydroxy moiety in one terminal in HCQ, both act as a weak base that can change the pH of acidic intracellular organelles including endosomes/ lysosomes, essential for the membrane fusion. It is believed that both agents could be effective tools against SARS-CoV-2. The addition of hydroxyl molecule makes HCQ less permeable to the blood-retinal barrier and allows faster clearance from retinal pigment cells, thereby suggesting a lesser risk of retinal toxicity with HCQ, as compared to chloroquine.

Furthermore, the narrow therapeutic and safety index margin with chloroquine makes HCQ a safer option than chloroquine. The antiviral activity of CQ and HCQ has been identified in the *in vitro* studies and the growth of many different viruses has been inhibited in the cell culture line by both the agents, including the SARS coronavirus. Mice studies have also demonstrated the activity of these agents against human coronavirus OC43, entero-virus EV-A71, Zika virus, and influenza A (H5N1). Chloroquine is a cheap and safe drug that has been used for more than 70 years and thus, it is potentially clinically applicable against COVID-19 [9-11].

Remdesivir: Remdesivir (GS-5734) is abroad-spectrum small-molecule antiviral drug which has activity against RNA viruses, including Coronaviridae (such as SARS-CoV, MERS-CoV and strains of bat coronaviruses capable of infecting human respiratory epithelial cells), Paramyxoviridae (such as Nipah virus, respiratory syncytial virus, and Hendra virus) and Filoviridae (such as Ebola virus).

Originally developed to treat Ebola virus infection, remdesivir is a prodrug of the parent adenosine analog, GS-441524, both of which are metabolized into an active nucleoside triphosphate (NTP) by the host. The parent nucleoside, GS-441524, has shown antiviral activity against SARS-CoV, Marburg virus. As a nucleoside analog, remdesivir acts as an RdRp inhibitor, targeting the viral genome replication process. The RdRp is the protein complex CoVs use to replicate their RNA-based genomes. After the host metabolizes remdesivir into active NTP, the metabolite competes with adenosine triphosphate for incorporation into the nascent RNA strand. The incorporation of this substitute into the new strand results in premature termination of RNA synthesis, halting the growth of the RNA strand after a few more nucleotides are added.

Although CoVs have a proofreading process that is able to detect and remove other nucleoside analogs, rendering them resistant to many of these drugs, remdesivir seems to outpace this viral proofreading activity, thus maintaining antiviral activity. The first COVID-19 patient in the USA was successfully treated with remdesivir for the progression of pneumonia on day 7 of hospitalization. Phase 3 human trials have been initiated to evaluate its efficacy in patients with SARS-CoV-2infection [12, 13].

Lopinavir and Ritonavir: The lopinavir-ritonavir combination is a fixed-dose medication for the prevention and treatment of HIV infection. The cytochrome P450 inhibitory effects of ritonavir prolonged the half-life of Lopinavir and extended its protease inhibitory action on the HIV replications.

It has been reported that ritonavir and lopinavir can bind to the endopeptidase C30 of SARS-CoV2 protease, which is evaluated by molecular models. This suggests that lopinavir-ritonavir may exert an antiviral effect by inhibiting the protein synthesis of the SARS-CoV2. In addition, several lines of evidence showed that treatment with lopinavir-ritonavir alone or in combination with other antiviral drugs was shown to improve the outcome of severe patients with SARS or MERS by ameliorating ARDS. Given that SARS-CoV2 is similar to these two viruses, lopinavir-ritonavir may have a beneficial effect on COVID-19.

Reports suggest that many patients have positively responded to the lopinavir-ritonavir drug combination and it should be evaluated further to prove the efficacy and safety [14].

Favipiravir: Favipiravir was developed as an anti-influenza drug in Japan. Among the anti-viral agents, Favipiravir has broad spectrum of activity towards RNA-viruses, influenza viruses, rhino-viruses, respiratory syncytial viruses.

Favipiravir was chosen to treat the lethal ebola virus epidemic in West Africa in 2014. Favipiravir is mainly incorporated in the salvage pathways for purine nucleotides through the purine phosphori-bosyl-transferases and it is further phosphorylated to Favipiravir-triphosphate as the substrate for viral RNA-dependent RNA polymerases (RdRp). Favipiravir is evaluated as a broad-spectrum anti-RNA virus drug and its efficacy has been evaluated at the cellular level and was used as a treatment option for ebola patients and it could be a great option for covid-19 patients [15].

Ribavirin: Ribavirin is a nucleoside analogue, having broad antiviral activity. It can prevent replication of RNA and DNA viruses by suppressing the activity of inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine triphosphate (GTP). Ribavirin was widely used to treat SARS patients with or without concomitant use of steroids during the outbreak of SARS in Hong Kong. Thus, Ribavirin could be considered as an effective treatment option for SARS-CoV2 [16].

Arbidol: Arbidol is an antiviral drug against the influenza infection, which is widely used in Russia and China. Arbidol and arbidol mesylate were shown to have a potent inhibitor effect in reducing the reproduction of SARS virus *in-vitro*. Low-level evidence included retrospective cohort, case

reports, and case series revealed that arbidol alone or combined with anti-viral drugs produced certain benefits in the treatment of COVID-19 pneumonia.

Currently, many randomized clinical control trials are carried out on studying the efficacy of arbidol on COVID-19 pneumonia in China.

Tocilizumab: Tocilizumab is a recombinant humanized monoclonal antibody against human interleukin 6 (IL-6) receptor of immunoglobulin IgG1 subtype. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signal transduction.

It has been approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. In addition, it has also been reported that it plays a certain role in Castleman disease and Crohn's disease. It is worth noting that tocilizumab is effective in the treatment of severe CRS patients. The FDA of the United States approved tocilizumab for the treatment of CRS caused by CAR-T (Chimeric Antigen Receptor T-Cell Immunotherapy) therapy.

SARS-CoV-2, SARS and MERS are coronaviruses and CRS of varying degrees have occurred in severe patients with SARS and MERS. All of them had high expression of IL-6. Currently, a small sample clinical trial in China has shown good efficacy in tocilizumab. Finally, although from the analysis of COVID-19's possible mechanism and small sample clinical data, tocilizumab has a better efficacy [17].

Ivermectin: Ivermectin is a broad-spectrum anti-parasitic agent with FDA-approved. In recent years, along with other groups, ivermectin has shown to have *in-vitro* anti-viral activity against a broad range of viruses. Originally identified as an inhibitor of the interaction between the human immune deficiency virus-1 (HIV-1), importin (IMP) α/β1 heterodimer, and the integrated protein (IN) responsible for IN nuclear import. Ivermectin inhibit IN nuclear import and HIV-1 replication. The causative agent of the current COVID-19 pandemic, SARS-CoV-2, is a single-stranded positive-sense RNA virus that is closely related to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV).

Studies on SARS-CoV proteins have revealed a potential role for IMPα/β1 during infection in the signal-dependent nucleocytoplasmic shutting of the SARS-CoV Nucleocapsid protein, that may impact host cell division. The SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMPα/β1 on the rough ER/Golgi membrane. Taken together, these reports suggested that ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2 [18].

Traditional Medicine: In India, the traditional system of medicine was followed for several hundred years for the treatment of medicines. Siddha, Ayurvedha, Unani, Homeopathy were the various systems of medicine followed in our country. Department of AYUSH promotes Siddha and other traditional systems of medicines for the treatment of Covid-19. It recommends the use of formulations like Nilavembu Kudineer, Kaba Sura Kudineer Choornam, and Maramanjal Kudineer Choornam for the effective treatment of Covid-19.

Docking studies of Kaba Sura Kudineer Choornam were carried out for the enzymes RdRp and CVMP, which are the important targets for the replication of RNA viruses like Covid-19. Docking was studied for 74 compounds. Out of this 74, 50 compounds produced results against CVMP and 42 compounds showed against SARS-Cov2 RdRp. The active constituents can be taken as a lead molecules for the development of a new drug for the effective treatment of Covid-19 [19].

Molecular docking studies of Maramanjal Kudineer Choornam was carried out for 74 phytoconstituents against the targets Covid-19 main protease and SARS CoV2 RdRp. The molecular docking study was carried out by using MGL Tools 1.5.6. Many of the active constituents showed an excellent binding affinity with these enzymes. Further, the potential legends can be taken as lead molecules for the Covid-19 drug development process [20].

Glycyrrhizin, an active component of liquorice roots in traditional Medicine, could effectively inhibit the replication of SARS-associated coronavirus *in-vitro.* Further, high doses of glycyrrhizin have been used in clinical trials, and the drug was reported to be clinically effective for

the treatment of SARS at that time. Recently, glycyrrhizin was predicted to have the ability to bind ACE2 with potential anti- COVID-19 effects. Hesperidin, a well-known traditional medicine, is a natural predominant flavonoid found in citrus fruits. Hesperidin dose-dependently suppresses the cleavage activity of the 3C-like protease (3CLpro) of SARS-CoV in cell-free and cell-based assays. Also, hesperidin was reported to have the potential to inhibit ACE2, therefore, block the infection of SARS- CoV2.

Baicalin, another traditional herbal medicine, is a flavone isolated from *Scutellaria baicalensis.* It has been shown that baicalin has antiviral activity against 10 clinical isolates of SARS-CoV by neutralization tests. In addition, quercetin is a plant flavone that is widely used in traditional medicine was reported to exert antivirus effects by inhibiting the 3CLpro of SARS-CoV and blocking the entry of SARS-CoV into host cells.

Therefore, these studies suggest that traditional medicine also plays a key role in the prevention and treatment of COVID-19 pneumonia [21-23].

Convalescent Plasma Therapy: Convalescent plasma (CP) therapy immunotherapy used as prevention and treatment of many infectious diseases for more than one century. Over the past two decades, CP therapy was auspiciously used in the treatment of SARS, MERS, and 2009 H1N1 pandemic with acceptable efficacy and safety. Antiviral antibodies (IgG, IgA, IgM, IgE, and IgD) produced in convalescent plasma from recovered patients can effectively treat patients with viral infections.

It has been reported that a small number of SARS-CoV-infected patients in Taiwan and Hong Kong received the treatment of convalescent plasma during the early course of the disease with certain clinical benefits, including a reduction of plasma viral load from ~105 copies/ml to undetectable levels 24 h after plasma transfusion. Hence, convalescent plasma therapy appears to be promising in the treatment of SARS-CoV2 [24, 25].

CONCLUSION: From the review of this study, the information obtained may be useful as a reference and helpful for researchers for further investigation and treatment ofSARS-CoV2.

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