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LETTERS

Clinical status of potential drugs used for COVID-19 treatment and recent advances in new therapeutics - A review

Kalpa Mandal,[1] Meenakshi Singh,[2] Charu Chandra,[1] Indraj Kumawat[1]

[1]Department of Chemistry, Dyal Singh College, University of Delhi, Delhi. India. [2]Department of Chemistry, Galgotias University, Greater Noida, UP, India

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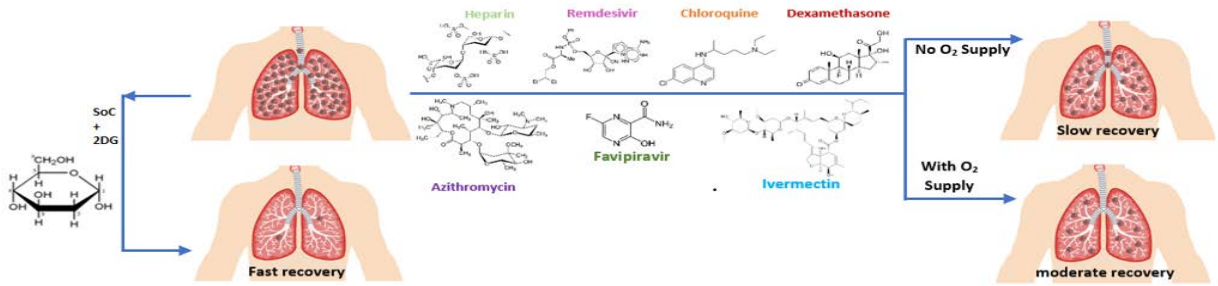
ABSTRACT



COVID-19, a perilous disease caused by SARS-CoV-2, has brought a massive damage to humankind, and turned into a global catastrophe. It was first reported in Wuhan, China in December 2019 and since then has been a constant source of worry for the scientists and the medical world, due to the carnage it has caused globally. Extensive clinical studies are being carried to explore drug therapy and prophylaxis to combat this pestilence. It is still an excessively big challenge for the scientists and pharmacological industry to develop potential drugs for the treatment of this deadly virus. At present though no specific drug has been identified as a perfect cure for this zoonotic disease, medical practitioners are using the therapy of repurposing of drugs for the treatment. Systemic research was carried out through e-resources to identify drugs for the treatment of COVID-19. A recent proposal of 2-DG drug as a cure for COVID-19 has also been discussed in this review.

Keywords: COVID-19, SARS- CoV-2, Drugs, clinical trials, 2-DG,

INTRODUCTION

In December 2019, China reported an unusual respiratory disease in the city of Wuhan which created havoc all around the world and turned into a global catastrophe.[1] It was investigated to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was named as corona virus disease (COVID-19) by WHO. This pneumonia related disease was discovered to be originated from bats.[2] On 30th January 2020, it was announced as a public health emergency of international concern and declared as a pandemic on 11 March 2020 by WHO. It is one of the deadliest pandemics in the history of mankind with more than 191,148,056 confirmed cases and 4,109,303 deaths till 21.July.2021 (Figure 1 and 2).

From its origin in China, it spread all over the globe at an exponential rate. After China, Europe became highly infected with several cases in Spain and Italy. Very soon, every country in the world became infected by this deadly disease.[3] With no specific cure and solution for this disease, the entire world was in great panic and threat.

Virologic studies and epidemiology suggests that transmission of this disease occurs from symptomatic as well as asymptomatic people[4] to others in close vicinity by respiratory droplets, or by close contact with infected person[5] or by contacting contaminated surfaces and objects. Patients with COVID-19 experience symptoms that are similar to those of other common disorders. Many patients with mild versions of the condition are told not to go the hospital or get a tests done, since they can recuperate at

*Dr Kalpa Mandal, Department of Chemistry, Dyal Singh College (University of Delhi), Lodhi Road, New Delhi.
Tel: 9811112382
Email: kalpamandal@dsc.du.ac.in

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home. A huge percentage of the population is asymptomatic.[6] Infected people are very contagious and can spread the disease even though they may be asymptomatic, which emphasises the importance of isolating and testing frequently.[7] Symptoms of this disease include fever, coughing, irritation in throat, loss of smell or taste, sore throat, headache, body ache, congestion, nausea, diarrhea, breathing problem, pneumonia, liver problem and heart problems.[8] Respiratory failure owing to alveolar injury might lead to the death of the patient[9] SARS-CoV-2 can also invade the brain as its ribonucleic acid has been detected in the cerebrospinal fluid (CSF) of COVID-19 patients. So, blood, brain, and CSF becomes potentially infectious.[10] It was also observed that the RNA of this severe acute respiratory syndrome corona virus 2 was detected in the blood donations.[11]

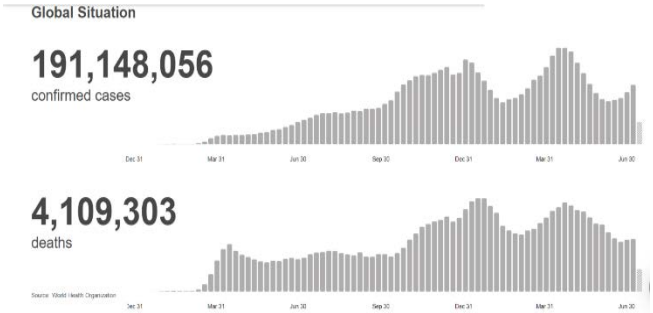


Figure 1. Graphical representation of COVID-19 cases till 21st July 2021 (source: World Health Organization)

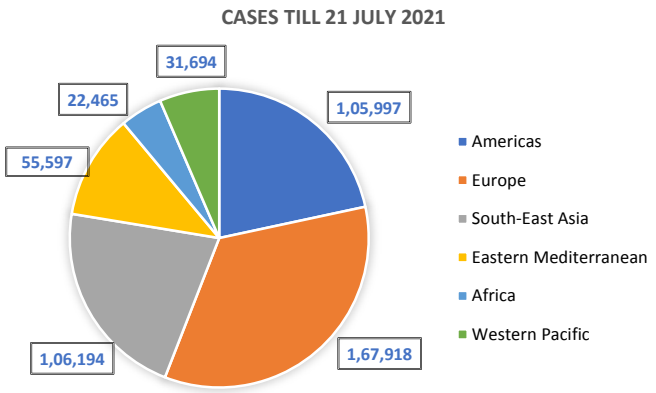


Figure 2. Region wise distribution of corona cases till 21 July 2021 (Source World Health Organization).

Initial step taken by government of various countries to prevent transmission of this disease, was to impose 'lockdown' to prevent people from meeting each other. Though this helped to some extent, but it could not be maintained for a long period of time as day-to-day essentialities had to be procured from the market. Many people working on daily wages started suffering from hunger, anxiety, and jobless situation. An excessively big challenge on the scientific community of the world was to develop drug/ vaccine as a cure for this disease. But till a breakthrough would come, medical practitioners took to repurposing of drugs as a curative therapy for COVID-19. To prevent additional outbreaks and cure of infections, therapeutic measures are being developed.[12] At the same time, several clinical trials and research are going worldwide to obtain perfect treatment for COVID-19. One such international trial is 'Solidarity', launched by World Health Organization and its partners, aimed to find an effective treatment for COVID-19. It is spread over 30 countries with approximately 12000 patients in 500 hospitals. It emphasizes its study on the effect of various drugs on COVID patients to know about three important outcomes: duration of hospital stays, need for assisted ventilation and mortality. The trial also compares the emerging treatments with the standard of care to know its efficacy against this disease.

HISTORY

Coronaviruses are from the family *Coronaviridae* of the order *Nidovirales.*[13,14] They are divided into four genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus, and Delta coronavirus. While the alpha corona virus and beta coronavirus attacks on mammals exclusively, the gamma and delta variants have a wider range of host which includes bird species.[15,16] Bats are thought to be reservoir hosts for its primogenitors in terms of the origin of SARS CoV viruses.[17] Though RaTG13 obtained from Rhinolophus affinis bat is 96 percent similar to SARS-CoV-2 in terms of overall identity, its spike differs in the RBD, suggesting that it may not bind to human ACE27 efficiently[18] Human corona viruses were first isolated in mid 1960s.[19] There are around seven corona viruses that can infect humans.[20] Common are HCoV-NL63,[21] HCoV-229E,[22] HCoV-OC43[23] and HKU1.[20] These mainly cause mild upper tract respiratory infections but are more severe in infant and elderly people.[24–27] Other human corona viruses are MERS-CoV,[28] SARS-CoV and SARS-CoV-2 which also cause severe respiratory pathologies.[29]

STRUCTURE AND ENTRY MECHANISM OF SARS-COV-2 VIRUS IN HOST CELL

Corona virus when viewed under electron microscope shows spike proteins[30] on its surface that gives the look of a crown and therefore, the name corona virus (Corona in Latin means Crown). (Figure 3).

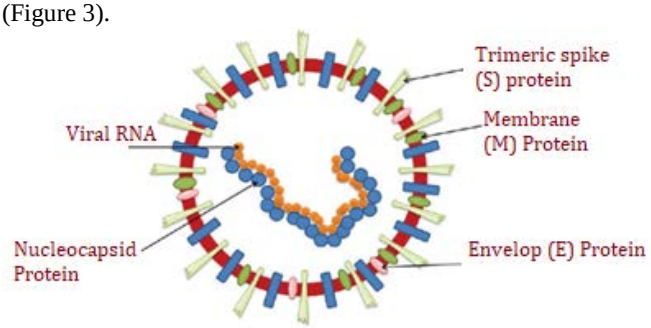


Figure 3. Structure of corona virus. Reproduced from ref [31] with permission.

Its average diameter varies from 80 nm to 120 nm[32] and contains different kinds of glycoproteins attached directly to its lipid bilayer surface. The Membrane protein (M), Spike protein (S), and Envelope protein (E) are embedded on the surface of the virus.[32] The Spike Proteins are in the form of large protrusions on the surface which directs the entry of virus into the host cell. It

has two subunits - S1 and S2. The S1 subunit forms head of the spike and catalyse its attachment to the cell by its receptor binding domain while its S 2 subunit instils fusion inside the cell. In the active state of S protein, three S1 subunits are attached to two S 2 subunits. The two subunits remain noncovalently linked when present on the surface until they attack the host cell membrane.[33] Inside the virus is its genetic material- the single positive stranded RNA genome which is encapsidated inside a helical capsid formed by the nucleocapsid protein (N). The genome size for coronaviruses ranges from 26.4 to 31.7 kilobases.[34]

The cell entry mechanism of SARS-CoV-2 has been extensively studied. The spike protein attacks the host through \the receptor binding domain of S1 subunit that recognizes a specific receptor- Angiotensin converting enzyme receptor-2 (ACE-2) on the host cell and enters by endocytosis or its direct fusion with the host cell.[35] Once the virus enters the cell, the release and uncoating of its genomic RNA takes place. The viral genomic RNA contains open reading frames ORF1a and ORF1b genes which produces two polyproteins pp1a and pp1b[36] that takes control over the host ribosome for its own translation.[37] pp1a and pp1b are involved in formation of replication transcription complex. (Figure 4)

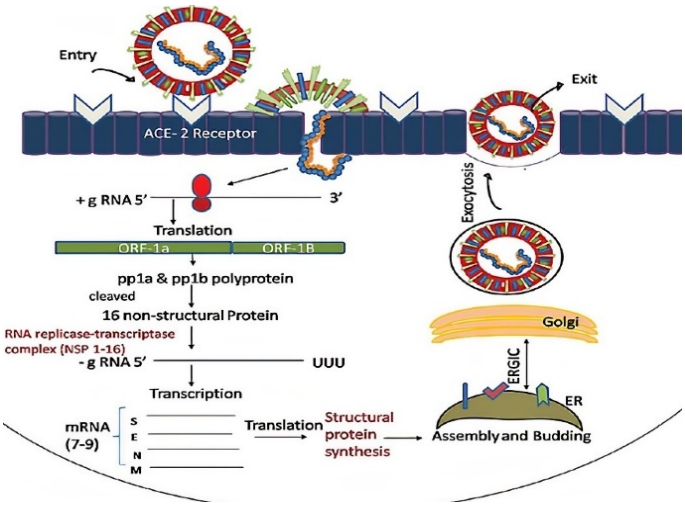


Figure 4. The life cycle of SARS-CoV-2 in host cells. Reproduced from ref [31] with permission.

The RNA is translated to produce 16 non-structural proteins (NSPs).[38] NSPs provides favourable cellular conditions for viral infection and viral mRNA synthesis.[39] It thus hijacks the host gene synthesis and regulates viral protein production.[40] The main replicase transcriptase protein is RNA-dependent RNA Polymerase (RdRp). This produces the genome of viral RNA as well as building blocks of the virus like capsids, spike proteins, envelope protein and membrane protein. All these takes place in endoplasmic reticulum-Golgi body intermediate compartment (ERGIC), which then interacts with N-encapsidated protein to produce newly genomic RNA. Virions are then finally secreted from the infected cell by exocytosis.[16]

In this review article we have discussed a few drugs with their mechanism of action, clinical trials, and their outcomes, as WHO has been releasing guidelines for the usage or discontinuation of drugs for curing corona virus disease.

DRUG CANDIDATES- THERAPEUTIC POTENTIAL

Since the outbreak of this disease in December 2019 in Wuhan, China, scientists, and researchers are trying hard for development of therapeutic drugs for COVID-19. Heterocyclic molecules are important part of drugs. Therefore drugs containing different heterocyclic moieties are being repurposed for treating COVID-19.[41] Currently there is no specific drug for treatment of this disease.[42] In comparison to the de novo drug discovery method, drug repurposing is a technique of identifying new uses for licensed or investigational medications. It is regarded a very effective strategy for drug discovery because it takes less time and money to locate a therapeutic agent.[43] As our understanding of COVID-19 virology and clinical manifestations improves, the number of possible pharmaceutical targets will also grow.[44] It is estimated that 75% of currently available medications can be repurposed to treat a variety of disorders.[45] Presently the Medical practitioners have taken up the path of repurposing of pre-existing drugs whose mechanism, dosage, characteristics, cytotoxicity, and efficacy are known, for treating patients suffering from corona virus. Some of the drugs under various categories are discussed below.

ANTIMALARIAL

Chloroquine and Hydroxychloroquine

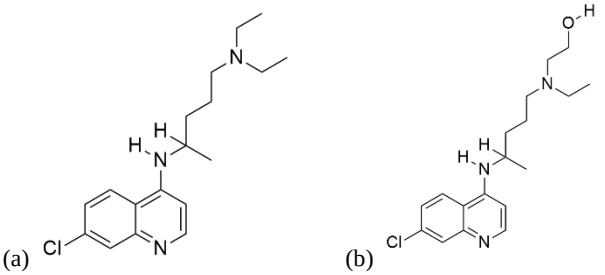


Figure 5. Chemical structure of (a) Chloroquine and (b) Hydroxychloroquine**.**

Chloroquine and hydroxychloroquine are aminoquinolines. In Hydroxychloroquine, one of the N-ethyl groups is hydroxylated at 2 positions. Both have been used since long against malaria. Chloroquine was first approved by the FDA in 1949 for the treatment of malaria. Chloroquine is also used for extraintestinal amebiasis. Approved in 1955, hydroxychloroquine, is typically favoured over chloroquine because it has less side effects. Hydroxychloroquine is known for its anti-inflammatory properties and has been used for malaria, systemic lupus erythematosus and rheumatoid arthritis. Both chloroquine and hydroxychloroquine have immunomodulatory effects. The FDA originally approved this drug for emergency use in treatment of COVID-19 patients.

The invitro studies of these drug have shown good results as an antiviral agent. Studies have shown that chloroquine and its more active derivative hydroxychloroquine acts by different

mechanisms to prevent SARS-CoV-2 infection. Chloroquine inhibits endocytosis[46] [Figure 6(a) &6(b)].

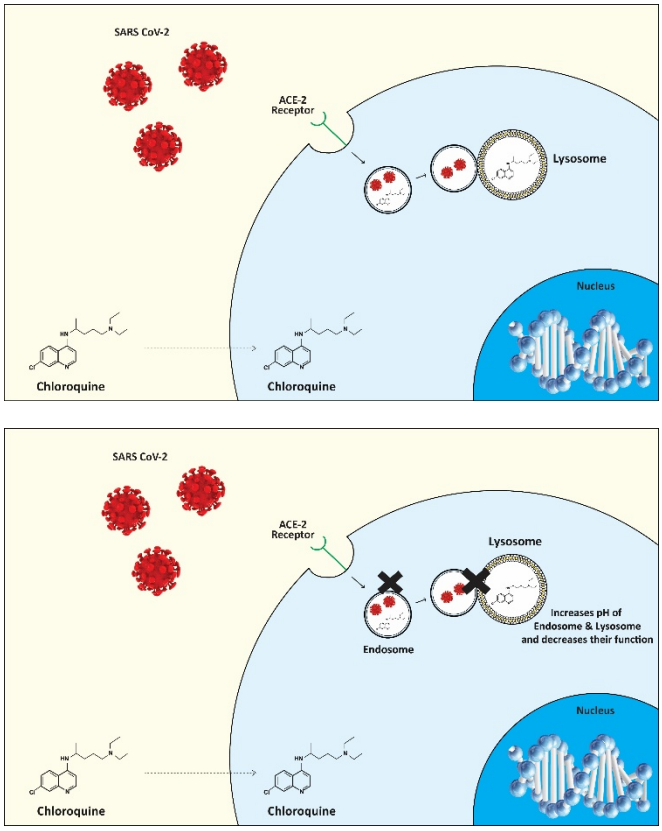
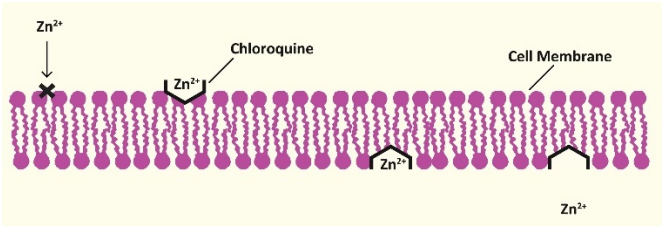


Figure 6. (a) & (b). Schematic representation showing chloroquine entering the cell and then into endosome and lysosome (containing corona virus), increasing its pH and preventing endocytosis.

The corona virus attacks the host cell and enters endosome. From the endosome it infuses into the lysosome from where it spreads in the cell. Chloroquine hampers this process. Since Chloroquine and hydroxychloroquine are alkaline, they increase the endosomal and lysosomal pH (these are acidic) and decrease their functioning and thus prevents endocytosis.

Chloroquine acts as zinc ionophore[47] [Figure 7(a) & 7(b)]. Since Zinc ions are unable to pass through the plasma membrane directly, this is facilitated by chloroquine. When corona virus enters in the cell, it produces RNA dependent RNA polymerase (RdRp) that is involved in viral multiplication . When zinc goes inside the cell with the help of chloroquine, it attacks on RdRp and prevents replication of viral RNA.[48] Thus, an increase in concentration of zinc, decreases the viral RNA.

Sialic acid is present on the surface of the host cell and found close to ACE-2 receptor. Chloroquine binds with sialic acid and gangliosides with great affinity[49] (Figure 8). Studies showed that, in the presence of CLQ [or its more active derivative, hydroxychloroquine (CLQ-OH)], the viral S protein is no longer able to bind gangliosides. The identification of this new mechanism of action of CLQ and CLQ-OH supports the use of these repositioned drugs to cure patients infected with SARS-CoV-2.



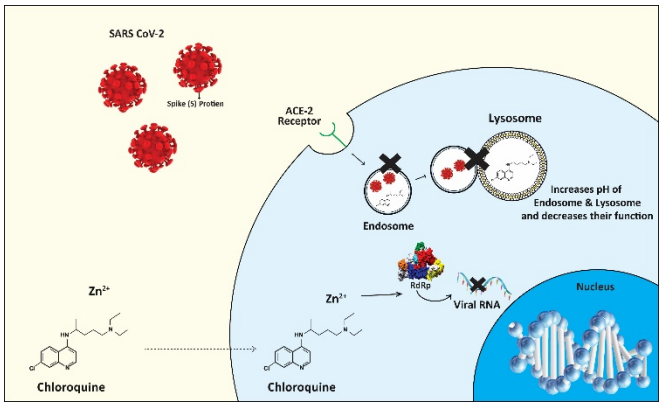


Figure 7. (a) Schematic representation of Zinc ions crossing plasma membrane (b) Schematic representation of Zinc ions preventing replication of viral RNA membrane with the help of chloroquine.

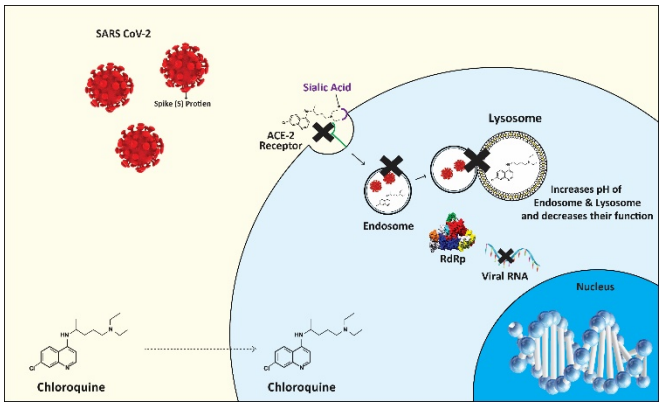


Figure 8. Schematic representation showing binding of chloroquine with sialic acid which prevents corona virus to bind to ACE2 receptor.

Clinical trials have shown mixed response for their use in treating COVID-19. Initially, though it was thought to be an extremely useful drug for corona virus but with further studies it was shown that chloroquine and hydroxychloroquine have limited effectiveness for curing COVID-19. Data shows that this drug does not reduce the mortality rate nor provide much help in improvement of recovery rate.[50] Therefore on 15th June 2020, FDA declared that these drugs were not suitable for treatment of COVID-19.

ANTIVIRAL DRUGS

Favipiravir

Favipiravir is a derivative of pyrazinecarboxamide and is used against RNA viruses. It was introduced in Japan in 2014 for therapeutic use against influenza virus.[51] It exhibits promising results against wide range of RNA viruses such as Ebola virus,

lassa virus, Rhinovirus, Arenavirus, Bunyavirus, flavivirus, MERS CoV and SARS CoV. Due to similarity of structure of SARS-CoV with SARS-CoV 2, favipiravir was also used in clinical trial for treatment of patients with COVID-19.[52]

Favipiravir works as a prodrug that is converted to its active form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP). Its mechanism involves selective inhibition of viral RNA-dependent RNA polymerase.[53]

This antiviral drug targets RNA-dependent RNA polymerase (RdRp) enzymes that are required for the transcription and replication of viral genomes. Favipiravir (T-705), a guanine analogue can effectively inhibit the RNA-dependent RNA polymerase of RNA virus, prevent its multiplication, and hence decreases the viral load (Figure10).

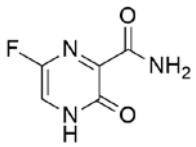


Figure 9. Chemical structure of Favipiravir

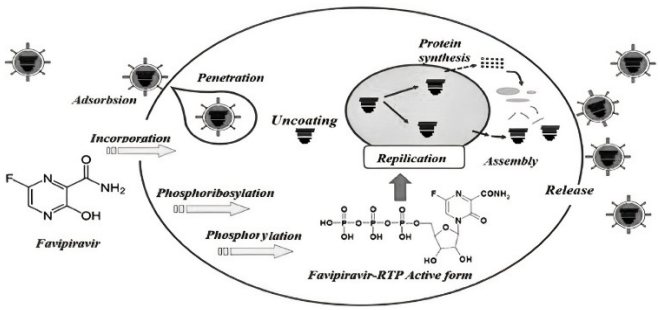


Figure 10. Schematic representation of the activation mechanism of favipiravirc. Reproduced from ref [54] with permission.

A clinical trial was carried out in Zhongnan Hospital of Wuhan University, China by Chen, and colleagues[55] to compare the efficacy and safety of favipiravir and arbidol. A group of 120 patients (116 assessed) were given favipiravir and another group of 120 patients (120 assessed) were given arbidol. The clinical recovery rate of day 7 with moderate patients of COVID-19 was found to be 51.6% in arbidol group and 61.20% in favipiravir group. This suggested that in treatment of COVID-19, favipiravir has significantly better result as observed from the viewpoint of progression of disease and viral clearance.

Other research has also shown positive results for the utlization of favipiravir for COVID-19. Since favipiravir is given orally, it is easy to be given to mildly ill patients or asymptomatic patients with COVID-19. However, more evidence and trials are required for assessing different doses and durations for different levels of severity of this disease.[56]

Remdesivir

In 2009, an American biopharmaceutical company Gilead Sciences, developed an antiviral drug Remdesivir to treat Hepatitis C that also showed potent activity against Ebola and MERS (Middle East Respiratory Syndrome).[57] Remdesivir (also known as GS 5734) has shown to have in vitro activity against SARS -CoV-2 and other coronaviruses (SARS-CoV, MERS-CoV).[58] During the corona virus outbreak, this drug was found to be useful in treatment of COVID -19, but along with a combination of vitamin supplements, steroids, oxygen therapy and blood thinners at appropriate stages.

FDA approved the use of this drug for COVID-19 in October 2020, based on the analysis of three clinical trials of hospitalized patients. It was a randomized, double-blind, placebo-controlled clinical trial with remdesivir, to know about the duration of recovery from COVID-19. It was observed that remdesivir was better than placebo in reducing recovery time in adults who were hospitalized and there is evidence of recovery with less infection in lower respiratory tract.[59]

Remdesivir is a prodrug of an adenosine tri phosphate (ATP). Inside the body, it metabolizes into its active form GS 441524 which is an adenosine analogue. The RNA dependent RNA polymerase picks up GS 441524 and incorporates it in the viral RNA strand.[60] It works by preventing viral exoribonuclease from proofreading viral RNA-dependent RNA polymerase (RdRp), causing viral RNA transcription to be prematurely terminated. This strand then becomes defective and thus viral RNA synthesis, and its multiplication stops. (Figure 12)

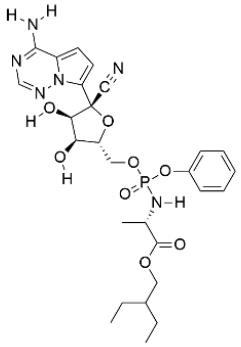


Figure 11. Chemical structure of Remdesivir

Second trial was a randomized open label multi-center clinical trial on patients with moderate COVID-19 in which comparison was made on treatment with remdesivir for 5 days and remdesivir for 10 days with the standard of care treatment. The third randomized trial included same treatment as the second trial but with severe COVID-19 patients.[61] Results showed that there was no remarkable difference between the 5 days and 10 days course of remdesivir.

According to results obtained from the open-label, randomized SOLIDARITY trial, it was found that remdesivir did not improve mechanical breathing requirements, clinical improvement time, mortality, or other significant patient outcomes. The results were of low or very low certainty and absence of sufficient data could not justify the usage of remdesivir as sure cure for COVID-19. Therefore, World Health Organization, on 20 November 2020, suggested conditional usage against using remdesivir in hospitalized COVID-19 patients. But that of the results from the World Health Organization-sponsored SOLIDARITY trial states that Remdesivir does not seem to defeat the clinical benefits of COVID-19 in hospitalized patients.

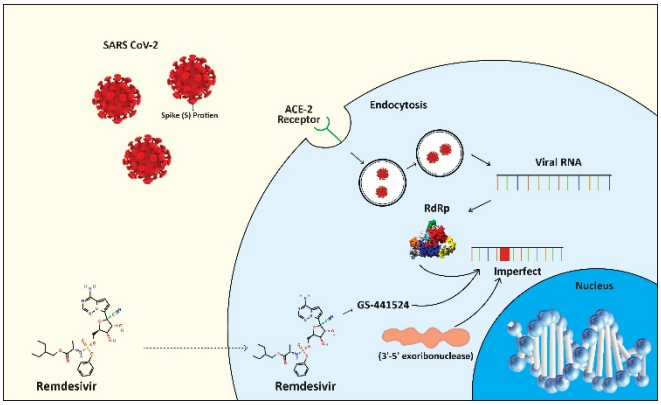


Figure 12. Schematic representation of activation mechanism of Remdesivir and its role in terminating viral RNA transcription.

ANTIBIOTIC

Azithromycin

Azithromycin is a broad spectrum azalide antibiotic obtained from erythromycin. It is from macrolide antibiotic class with bactericidal and bacteriostatic properties.

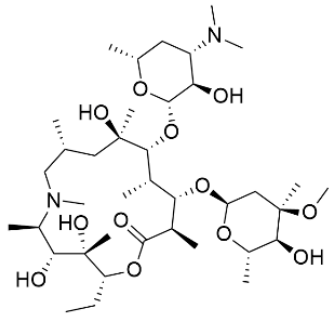


Figure 13. Azithromycin

As a result of positive treatment outcomes in other viral pneumonias, azithromycin gained importance. It has therefore been adapted as repurposed drug and is given for treatment to COVID-19 patients to prevent the secondary complications that arises due to bacterial infection. It also possesses anti-inflammatory properties that reduces exaggerated response due to COVID-19. Studies have shown that azithromycin in combination with hydroxychloroquine has given better results in treating patients with COVID-19[62] (Figure 14).

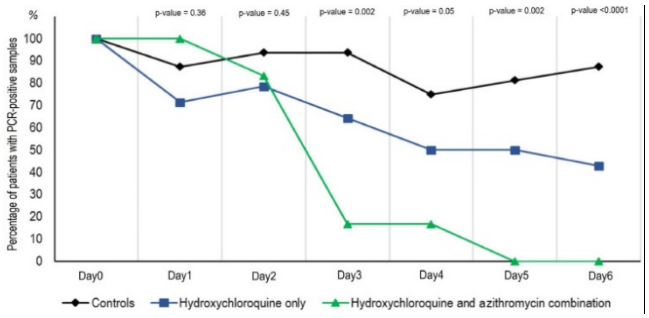


Figure 14. Showing better results in COVID-19 patients who have been given Azithromycin in combination with hydroxychloroquine than Hydroxychloroquine alone or SoC in COVID-19 patients. Adapted from Ref [62] with permission.

The combined drug treatment was given to a group of 6 PCR positive patients for 5 days with the dosage of Azithromycin 500mg on day 1 followed by 250 mg per day for next 4 days and for hydroxychloroquine 600mg per day for 10 days. The result

showed that by day 5 all the patients cleared virus. But in another study with 11 patients, who were given this combination in which 1 died, two were shifted to ICU, one developed heart toxicity. 2 out of 10 cleared viruses in 6 days. A randomized clinical trial was conducted in Brazil with 447 patients who were given 500 mg Azithromycin as well as standard of care for 10 days including hydroxychloroquine or only standard of care. It was observed that there was no remarkable improvement on clinical outcome by using Azithromycin.[63]

ANTIHELMINTIC

Ivermectin

Ivermectin is a broad-spectrum drug approved by FDA as an anti-parasitic agent. It is also known to be useful against various viruses[64] like HIV virus, Dengue virus, Influenza virus, West Nile Virus, Pseudorabies virus etc Since Ivermectin is known for its role in many biological mechanisms, it can therefore be utilized in treating COVID-19 along with other types of positive-sense single-stranded RNA viruses.[65]

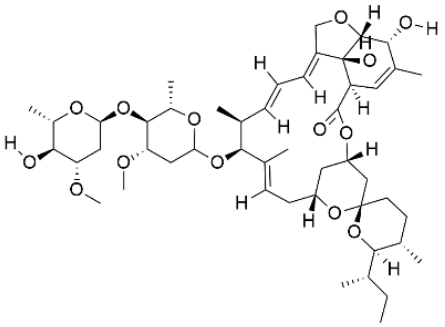


Figure 15. Chemical structure of Ivermectin

The virus, using its spike protein enters the host cell through ACE-2 receptor and in the cytoplasm, it releases its RNA. The virus hijacks the hosts ribosomes to make its long polypeptide chains. It produces a very important protein RdRp which helps in its multiplication. Since the virus cannot enter the nucleus directly, they use the special carrier molecules Importin α/ Importin β1 (IMP) α/β1 heterodimer to enter the nucleus through nuclear pore complex[66] (Figure 16). Inside the nucleus the viral-importin complex breaks apart and the viral protein can reduce the host cell antiviral response which leads to enhancement of the infection. The role of Ivermectin is that it works by binding to importin heterodimer, the nuclear transport protein[67] which is responsible for nuclear import of viral protein such as integrase protein (IN) and prevents viral protein from binding to importin and the viral complex is unable to enter the nucleus and thus causes reduction of antiviral response. That is, Ivermectin prevents host and viral proteins from being imported into the nucleus, which may prevent viral replication. Therefore, Ivermectin's nuclear transport inhibitory activity could be effective against SARS-CoV-2.

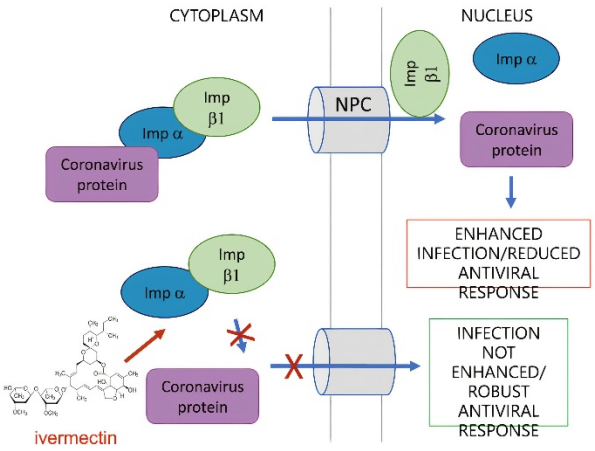


Figure 16. Schematic representation of Ivermectin proposed antiviral action on coronavirus. Adapted from ref [68] with permission.

In the in vitro studies conducted by Leon caly et al,[68] it was found that a single treatment of ivermectin is able to effect 5000-fold reduction of virus in 48 hours and decreases the viral load by 99.99%. Other in vitro studies have also revealed that ivermectin was found to inhibit SARS-CoV-2 viral replication.[69] To determine the role of ivermectin in rapidity and viral clearance of COVID-19 patients, a clinical trial (randomized, double blind, placebo-controlled trial) was conducted in Dhaka, Bangladesh with 72 hospitalized patients.[70] They were divided into three groups of 24 patients. One group was treated with ivermectin only (12 mg daily, for 5 days). Another group was treated with oral ivermectin along with antibiotic doxycycline (One dose of 12 mg ivermectin with 200 mg doxycycline on day 1, continued for next 4 days with 100 mg every 12 hourly), and the third was a placebo control group. No adverse drug interaction was observed. In another trial of 18 randomized control treatment with ivermectin, statistical data showed significant decrease in clinical recovery time and mortality.[71] Study revealed that viral clearance was faster in the patients treated with ivermectin alone as compared to the placebo group. This study shows the use of ivermectin to be good for COVID patients, but since it was for a very small group of patients, more research and evidence would be required to declare the usage of this drug.

CORTICOSTEROID

Dexamethasone

On 16 June 2020, the use of dexamethasone for COVID-19 patients suffering from severe respiratory symptoms was recommended in a press release for Randomized Evaluation of COVID-19 therapy (RECOVERY) trial. Randomly, 2104 patients[72] were given dexamethasone 6mg once a day and were compared to 4321 patients randomised with routine care. It was observed that dexamethasone decreased the death rate by about one-third in case of ventilated patients and by one fifth in rest of the patients receiving oxygen. There was no benefit among those patients who did not require respiratory support.

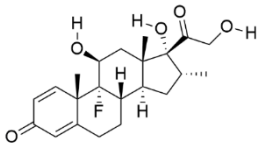


Figure 17. Dexamethasone

Dexamethasone is a type of synthetic steroid hormone produced in adrenal cortex. It belongs to glucocorticoid class of corticosteroids. It is known for its anti-inflammatory property as well as immunosuppressive impact and is therefore used in various diseases including asthma, pneumonia, chronic obstructive lung disease, different allergies (food allergy, drug allergy), multiple sclerosis relapses, skin problems, rheumatological diseases and many others. Also, its use has been indicated in previous coronavirus disease such as MERS (Middle East Respiratory Syndrome) and SARS (severe acute respiratory syndrome).[7374] But there are very few clinical studies available, indicating the usage of corticosteroids for treating the COVID-19 patients. Dexamethasone functions by inhibiting a pro-inflammatory gene which encodes for cytokines, chemokines, cell adhesion molecules as well as acute inflammatory response. Steroids help to modulate the immune response to the infection and try to bring it back to normal.

A clinical trial on 46 patients with severe COVID-19 disease was carried out, with 26 of them receiving intravenous methylprednisolone (Medrol) at a dose of 1–2 mg/kg/d for 5–7 days. The findings demonstrated a faster increase in oxygen saturation, a higher degree of absorption of the focus in chest CT, and lesser time to recover from hyperthermia.[75] Despite this, a study of 31 patients who received 11 doses of corticosteroids found no significant changes between treated and untreated patients.[76]

Consequently, it was concluded that under mild symptoms, glucocorticoids are not suitable for the treatment of COVID-19.[77] This may be due to these suppressing the cytokine storm.[78] As of now, according to WHO and the Centres for Disease Control and Prevention (CDC), Glucocorticoids should not be used in COVID-19 pneumonia unless there are certain concomitant clinical disorders, such as worsening of chronic obstructive pulmonary disease.[79]

ANTICOAGULANT

Heparin

COVID-19 has been reported with coagulatory activation, with increased risk of DIC (disseminated intravascular coagulation), DVC (Deep Venous Thrombosis) and PE (Pulmonary Embolism) in severe phase.[80] Experts have therefore recommended anticoagulants particularly heparin (low molecular weight unfractionated heparin) for patients with severe COVID-19. The thromboembolic symptoms therefore suggest the role of coagulopathy in the patients of COVID-19.[81] Clinical observations show that utilising the anticoagulant drug heparin reduces systemic symptoms induced by SARS-CoV-2 infection.[82] Heparin is a sulfur-rich glycosaminoglycan which has anticoagulant property. It also has immunomodulatory, anti-

inflammatory as well as anti-viral property which may be useful past the anti- coagulation.[83]

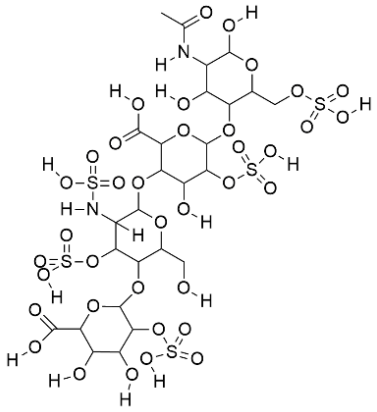


Figure 18. Chemical structure of Heparin

Upon binding to antithrombin III, it forms a complex heparin-antithrombin III, which inactivates thrombin and other clotting factors.[84] This stops polymerization of fibrinogen to fibrin and hence prevents formation of clots.

The spike protein of corona virus attacks the endothelium of blood vessels and damages it is causing inflammation. COVID-19 leads to elevated fibrinogen, elevated D dimer, elevated C reactive protein. These are all biomarkers for coagulation (a condition in which abnormal lumps of thickened blood clots are formed throughout the body, blocking small blood vessels) leading to increased risk of DIC (disseminated intravascular coagulation), DVC (Deep Venous Thrombosis) and PE (Pulmonary Embolism) in severe phase.[85] In a small cohort study with 44 patients, the use of heparin showed better coagulation parameters and improved immunity with increased lymphocyte counts as compared to control subjects.[86] A preprint article, discussing the RAPID trial of 465 COVID affected people, showed that patients with low molecular weight heparin had low incidence of death.[87] InTonji hospital, patients with severe COVID-19 were analysed retrospectively. 99 patients were given low molecular weight Heparin. Mortality was lower in heparin users than in non-heparin users.

Mortality was lower in heparin users than in non-heparin users.[88] Though, a lot of studies support the role of heparin in COVID-19, but it should be proved by clinical trials. Due to limited evidence, the clinical treatment guidelines do not recommend the use of heparin or other anticoagulatory drug for COVID-19.

RECENT ADVANCEMENTS

2-DEOXY- D- GLUCOSE :

The DRDO (Defence research and development organization) laboratory, Institute of nuclear medicine and allied Sciences (INMAS) (India), in collaboration with Dr Reddy's laboratories (DRL), Hyderabad, has proposed a repurposed drug, 2-deoxy-D-glucose indigenously developed to be used as an adjunct therapy against COVID -19. The drug can prove to be a gamechanger and bring about a phenomenal change in the scientific world with its fast action and high efficacy against COVID-19.

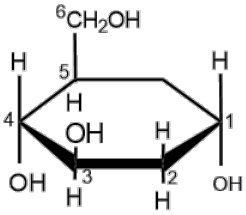


Figure 19. Chemical structue of 2-deoxy-D-glucose (2-DG)

This drug is a glucose analogue.[89] The oxygen at 2nd position of the glucose ring is removed and hence the name 2- deoxy-D-glucose[90] (Figure 19). Studies have proved that the infected cells have greater number of glut receptors on their surface than the normal cells. The drug is taken up more readily by the infected cells and gets selectively accumulated there.[91]

The 2-DG drug alters glycosylation of viral glycoprotein, inhibits energy production and viral multiplication, and renders it incapable of infecting human cells. It also reduces the dependence on supplemental oxygen. This molecule is also known for its therapeutic values as an anticancer agent[92]. This drug can be broadly classified as an antiviral drug. Upon accumulation in the infected cells, it chokes the glucose metabolism and arrests energy production. Hence it inhibits anabolic reactions required for viral multiplication and reduces re-infectivity of newly formed SARS-CoV-2 virus.[93] The action of 2DG is shown in Figure 20.

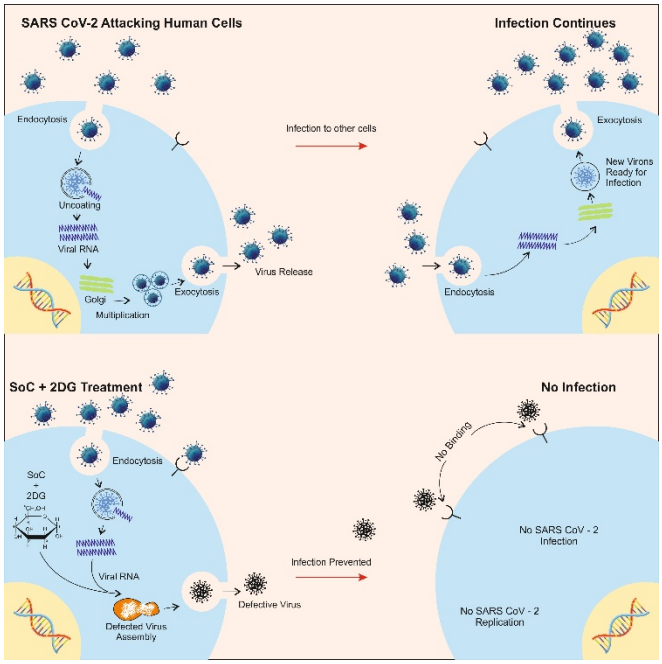


Figure 20. Accumulation of 2-DG in infected cells. Reproduced from ref [91] with permission.

In April 2020, the scientists of INMAS-DRDO & CCMB (Centre for cellular and molecular biology), Hyderabad, conducted the first phase of trials and found that this drug works effectively against SARS-CoV-2. In May 2020, the second phase

of trials was conducted on 110 patients. Phase 2a trials were conducted in six hospitals and phase 2b (variable doses) were conducted in eleven different hospitals across the country. Between November 2020 to March 2021, the third stage trials were carried out on 220 patients admitted in 27 different hospitals across the country. The patients were treated with 90 mg/kg/day along with standard of care against only standard of care (SoC). On third day almost 50% patients came out of oxygen supplement in comparison to 30% patients from SoC arm. A statistical difference of 20% was observed. The DCGI (The Drugs Controller General of India) granted permission for the use of 2-DG drug for mild and severely affected COVID-19 patients. Data from the third trial phase showed that the drug worked effectively in bringing down the symptoms of the patients and helped them in overcoming their dependence on supplemental Oxygen by day 3, indicating early relief from the disease. Now the prescribed dosage of this drug includes a Sachet of 2.34g to be dissolved in water and to be taken orally twice a day for a week and not more than 10 days. As of now, this drug has been approved for emergency use only. Due to lack of studies, on pregnant and lactating mothers, 2-DG should not be given to them. The advantage of this drug is that it is a generic medicine and can easily be produced on large scale. But there are few questions to ponder upon. Availability of few published data and the third phase trial conducted by INMAS-DRDO & CCMB does not mention about the benefits and side effects of this drug.

CONTROL TECHNIQUES

Various disinfection techniques are being considered at personal as well as hospital levels to bring about a decrease in the worldwide spread of SARS CoV-2.[94,95] The nano scale based medicine[96] and materials have been on frontier of evaluation to mitigration of this viral infection. Several studies have established that the UVC light has long been used for inactivation of airborne pathogens to prevent airborne transmission.[97] The short wavelength and high energy of UVC light has the great power for microbial disinfection. SARS CoV-2 has a fragile sensitive layer that is susceptible to heat and UV radiations. UVC can therefore be effectively used to curb the transmissivity of the highly infectious SARS CoV-2 virus.[98,99] Experiments have shown that bacteria become inactivated in far UVC light (207nm-222nm). David Welch et al have tried to show that airborne aerosolized viruses can be inactivated up to 95% even with the minimal dose of 2mJ/cm^2 of 222 nm UVC light.[100] Studies have also shown that 99.9 % of corona virus 229E and OC43 becomes inactive by 1.7 mJ/cm^2 and 1.2 mJ/cm^2 low doses of UVC light, respectively.[101] Analysis done by Fabrizio Nicastro et al suggests that solar UV-B/A light will also play a vital role in deciding strategies for the control of this pandemic.[102] UVC light finds its application in the sanitization of healthcare departments, respirators, medical machines, and personal protective equipment (PPE) as well. Apart from UV radiations, gaseous ozone has also been studied as a source of disinfection for both air and surfaces with varying volumes for small chambers to large rooms. The dosage and contact time are vital in establishing protocol for COVID 19.[103]

CONCLUSION

The review is based on newly published articles and papers on COVID-19. It suggests that the available data and clinical trials are not sufficient to prescribe any treatment as a cure for this disease. The scientific community and pharmacological companies are working day and night to overcome the challenge of curing this disease by prophylaxis strategies, repurposing of drugs, and developing new potential drugs and vaccines. The obstacle in developing a potent drug is the emergence of new variants due to fast-mutating ability of the virus. In the past one and half years, extensive studies have been carried out to understand the growth, development, multiplication, and transmission of this disease. DRDO's 2-DG drug can prove to be a game changer for the treatment. But there are few questions to ponder upon. Firstly, there is just one published data and no peer reviewed articles of this drug on human trials. Secondly, the third phase trials do not mention about the benefits and side effects of the drug. Therefore, still a lot of research and clinical trials are required to come up with a positive result. Though many efforts are being put towards inoculating the populace, but still there is an urgent need to develop potential therapeutics to effectively combat the fast-mutating SARS-CoV-2 pathogenicity.

REFERENCES

1. B. Gates. Responding to Covid-19 — A Once-in-a-Century Pandemic? *N. Engl. J. Med.* **2020**, 382 (18), 1677–1679.
2. P. Zhou, X. Lou Yang, X.G. Wang, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, 579 (7798), 270–273.
3. C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao. A novel coronavirus outbreak of global health concern. *Lancet* **2020**, 395 (10223), 470–473.
4. Y. Li, J. Shi, J. Xia, et al. Asymptomatic and Symptomatic Patients With Non-severe Coronavirus Disease (COVID-19) Have Similar Clinical Features and Virological Courses: A Retrospective Single Center Study. *Front. Microbiol.* **2020**, 11, 1570.
5. J.F.-W. Chan, S. Yuan, K.-H. Kok, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* **2020**, 395 (10223), 514–523.
6. M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli. Features, Evaluation, and Treatment of Coronavirus. *StatPearls* **2020**, No. Cdc, 19.
7. J.R. Larsen, M.R. Martin, J.D. Martin, P. Kuhn, J.B. Hicks. Modeling the Onset of Symptoms of COVID-19. *Front. Public Heal.* **2020**, 8 (Aug), 0473.
8. C. Huang, Y. Wang, X. Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, 395 (10223), 497–506.
9. G.E. Antonio, K.T. Wong, D.S.C. Hui, et al. Imaging of severe acute respiratory syndrome in Hong Kong. *Am. J. Roentgenol.* **2003**, 181 (1), 11–17.
10. T. Moriguchi, N. Harii, J. Goto, D. Harada, H. Sugawara. International Journal of Infectious Diseases Case Report A fi rst case of meningitis / encephalitis associated with. *Int. J. Infect. Dis.* **2021**, 94 (2020), 55–58.
11. L. Chang, L. Zhao, H. Gong, L. Wang, L. Wang. Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations.

Emerg. Infect. Dis. **2020**, 26 (7), 1631–1633.
12. S. Khan, R. Siddique, M.A. Shereen, et al. Correction for Khan et al., "Emergence of a Novel Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2: Biology and Therapeutic Options." *J. Clin. Microbiol.* **2020**, 58 (8), 1–10.
13. L. Enjuanes, F. Almazán, I. Sola, S. Zuñiga. Biochemical aspects of coronavirus replication and virus-host interaction. *Annu. Rev. Microbiol.* **2006**, 60, 211–230.
14. S. Perlman, J. Netland. Coronaviruses post-SARS: Update on replication and pathogenesis. *Nat. Rev. Microbiol.* **2009**, 7 (6), 439–450.
15. J. Cui, F. Li, Z.L. Shi. Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol.* **2019**, 17 (3), 181–192.
16. P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, V. Thiel. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat. Rev. Microbiol.* **2021**, 19 (3), 155–170.
17. W. Li, Z. Shi, M. Yu, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science (80-.).* **2005**, 310 (5748), 676–679.
18. R. Lu, X. Zhao, J. Li, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **2020**, 395 (10224), 565–574.
19. J.S. Kahn, K. McIntosh. History and Recent Advances in Coronavirus Discovery. *Pediatr. Infect. Dis. J.* **2005**, 24 (11), S223–S227.
20. P.C.Y. Woo, S.K.P. Lau, C. Chu, et al. Characterization and Complete Genome Sequence of a Novel Coronavirus, Coronavirus HKU1, from Patients with Pneumonia. *J. Virol.* **2005**, 79 (2), 884–895.
21. S. Abdul-Rasool, B.C. Fielding. Understanding Human Coronavirus HCoV-NL63~!2009-11-13~!2010-04-09~!2010-05-25~! *Open Virol. J.* **2010**, 4 (1), 76–84.
22. D. Hamre, J.J. Procknow. A New Virus Isolated from the Human Respiratory Tract. *Proc. Soc. Exp. Biol. Med.* **1966**, 121 (1), 190–193.
23. J.R. St-Jean, H. Jacomy, M. Desforges, et al. Human Respiratory Coronavirus OC43: Genetic Stability and Neuroinvasion. *J. Virol.* **2004**, 78 (16), 8824–8834.
24. R.A.M. Fouchier, N.G. Hartwig, T.M. Bestebroer, et al. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc. Natl. Acad. Sci.* **2004**, 101 (16), 6212–6216.
25. D. Hamre, D.A. Kindig, J. Mann. Growth and Intracellular Development of a New Respiratory Virus. *J. Virol.* **1967**, 1 (4), 810–816.
26. L. Van Der Hoek, K. Pyrc, M.F. Jebbink, et al. Identification of a new human coronavirus. *Nat. Med.* **2004**, 10 (4), 368–373.
27. A.R. Falsey, E.E. Walsh, F.G. Hayden. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. *J. Infect. Dis.* **2002**, 185 (9), 1338–1341.
28. H.J. Han, H. Yu, X.J. Yu. Evidence for zoonotic origins of Middle East respiratory syndrome coronavirus. *J. Gen. Virol.* **2016**, 97 (2), 274–280.
29. J.S.M. Peiris, Y. Guan, K.Y. Yuen. Severe acute respiratory syndrome. *Nat. Med.* **2004**, 10 (12S), S88–S97.
30. D. Kumar, V. Chandel, S. Raj, et al. In silico identification of potent FDA approved drugs against Coronavirus COVID-19 main protease: A drug repurposing approach. *Chem. Biol. Lett.* **2020**, 7 (3 SE-Research Articles), 166–175.
31. N. Kumar, T. Kanchan, B. Unnikrishnan, et al. Characterization of Rubia cordifolia L. root extract and its evaluation of cardioprotective effect in Wistar rat model. *Indian J. Pharmacol.* **2018**, 49 (5), 344–347.
32. P.S. Masters. The Molecular Biology of Coronaviruses. *Adv. Virus Res.* **2006**, 65 (06), 193–292.
33. K. Lalchhandama. The chronicles of coronaviruses: the electron microscope, the doughnut, and the spike. *Sci. Vis.* **2020**, 20 (2), 78–92.
34. P.C.Y. Woo, Y. Huang, S.K.P. Lau, K.Y. Yuen. Coronavirus genomics and bioinformatics analysis. *Viruses* **2010**, 2 (8), 1805–1820.
35. G. Simmons, P. Zmora, S. Gierer, A. Heurich, S. Pöhlmann. Proteolytic activation of the SARS-coronavirus spike protein: Cutting enzymes at the cutting edge of antiviral research. *Antiviral Res.* **2013**, 100 (3), 605–614.
36. A.J.W. Te Velthuis, S.H.E. Van Den Worm, E.J. Snijder. The SARS-coronavirus nsp7+nsp8 complex is a unique multimeric RNA polymerase capable of both de novo initiation and primer extension. *Nucleic Acids Res.* **2012**, 40 (4), 1737–1747.
37. C.C. Stobart, N.R. Sexton, H. Munjal, et al. Chimeric Exchange of Coronavirus nsp5 Proteases (3CLpro) Identifies Common and Divergent Regulatory Determinants of Protease Activity. *J. Virol.* **2013**, 87 (23), 12611–12618.
38. Y. Lim, Y. Ng, J. Tam, D. Liu. Human Coronaviruses: A Review of Virus–Host Interactions. *Diseases* **2016**, 4 (4), 26.
39. E. Prentice, J. McAuliffe, X. Lu, K. Subbarao, M.R. Denison. Identification and Characterization of Severe Acute Respiratory Syndrome Coronavirus Replicase Proteins. *J. Virol.* **2004**, 78 (18), 9977–9986.
40. K. Nakagawa, K.G. Lokugamage, S. Makino. Viral and Cellular mRNA Translation in Coronavirus-Infected Cells, 1st ed.; Elsevier Inc., **2016**; Vol. 96.
41. M. Khatri, P. Mago. Nitazoxanide/camostat combination for COVID-19: An unexplored potential therapy. *Chem. Biol. Lett.* **2020**, 7 (3), 192–196.
42. B.S. Chhikara, B. Rathi, J. Singh, P. FNU. Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. *Chem. Biol. Lett.* **2020**, 7 (1), 63–72.
43. T. Uttam Singh, S. Parida, M. Cholenahalli Lingaraju, et al. Drug repurposing approach to fight COVID-19. *Pharmacol. Reports* **2020**, 72, 1479–1508.
44. J. Sultana, S. Crisafulli, F. Gabbay, et al. Challenges for Drug Repurposing in the COVID-19 Pandemic Era. *Frontiers in Pharmacology*. 2020, pp 1–13.
45. F. Huang, C. Zhang, Q. Liu, et al. Identification of amitriptyline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. *PLOS Pathog.* **2020**, 16 (3), e1008341.
46. R. Delvecchio, L.M. Higa, P. Pezzuto, et al. Chloroquine, an endocytosis blocking agent, inhibits zika virus infection in different cell models. *Viruses* **2016**, 8 (12), 1–15.
47. J. Xue, A. Moyer, B. Peng, et al. Chloroquine is a zinc ionophore. *PLoS One* **2014**, 9 (10), 1–6.
48. A.J.W. te Velthuis, S.H.E. van den Worml, A.C. Sims, et al. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* **2010**, 6 (11).
49. J. Fantini, C. Di Scala, H. Chahinian, N. Yahi. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *Int. J. Antimicrob. Agents* **2020**, 55 (5), 105960.
50. P. Horby, M. Mafham, L. Linsell, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* **2020**, 383 (21), 2030–2040.

51. S.K. et al Furuta Y, Gowan B, Takahashi K. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *J. Pers. Soc. Psychol.* **2008**, 95 (2), 1045–1062.
52. M. Sada, T. Saraya, H. Ishii, et al. Detailed Molecular Interactions of Favipiravir with SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza Virus Polymerases In Silico. *Microorganisms* **2020**, 8 (10), 1610.
53. Z. Jin, L.K. Smith, V.K. Rajwanshi, B. Kim, J. Deval. The Ambiguous Base-Pairing and High Substrate Efficiency of T-705 (Favipiravir) Ribofuranosyl 5′-Triphosphate towards Influenza A Virus Polymerase. *PLoS One* **2013**, 8 (7), 1–10.
54. M. Ghasemnejad-Berenji, S. Pashapour. Favipiravir and COVID-19: A Simplified Summary. *Drug Res. (Stuttg).* **2021**, 71 (3), 166–170.
55. C. Chen, Y. Zhang, J. Huang, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. *medRxiv* **2020**.
56. T. Manabe, D. Kambayashi, H. Akatsu, K. Kudo. Favipiravir for the treatment of patients with COVID-19: a systematic review and meta-analysis. *BMC Infect. Dis.* **2021**, 21 (1), 1–13.
57. T.P. Sheahan, A.C. Sims, R.L. Graham, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci. Transl. Med.* **2017**, 9 (396), eaal3653.
58. M.L. Agostini, E.L. Andres, A.C. Sims, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio* **2018**, 9 (2), 1–15.
59. J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N. Engl. J. Med.* **2020**, 383 (19), 1813–1826.
60. M. Wang, R. Cao, L. Zhang, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* **2020**, 30 (3), 269–271.
61. J.D. Goldman, D.C.B. Lye, D.S. Hui, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N. Engl. J. Med.* **2020**, 383 (19), 1827–1837.
62. P. Gautret, J. Lagier, P. Parola, V.T. Hoang. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents* **2020**, 56 (1).
63. R.H.M. Furtado, O. Berwanger, H.A. Fonseca, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* **2020**, 396 (10256), 959–967.
64. F. Rocha, R. Leblanc, J. De Souza. Ivermectin: an award-winning drug with expected antiviral activity against COVID-19. *J. Control. Release J.* **2021**, 329, 758–761.
65. F. Heidary, R. Gharebaghi. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J. Antibiot. (Tokyo).* **2020**, 73 (9), 593–602.
66. K.M. Wagstaff, H. Sivakumaran, S.M. Heaton, D. Harrich, D.A. Jans. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem. J.* **2012**, 443 (3), 851–856.
67. S.N.Y. Yang, S.C. Atkinson, C. Wang, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Res.* **2020**, 177, 104760.
68. L. Caly, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* **2020**, 178, 104787.
69. E. Rizzo. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **2020**, 393 (7), 1153–1156.
70. S. Ahmed, M.M. Karim, A.G. Ross, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int. J. Infect. Dis.* **2021**, 103, 214–216.
71. P. Kory. Review of the Emerging Evidence Supporting the Use of Ivermectin in the Prophylaxis and Treatment of COVID-19. *Front Line COVID-19 Crit. Care Alliance* **2020**, 318, 1–21.
72. P. Horby, W. Lim, J. Emberson, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* **2021**, 384 (8), 693–704.
73. L.J. Stockman, R. Bellamy, P. Garner. SARS: Systematic review of treatment effects. *PLoS Med.* **2006**, 3 (9), 1525–1531.
74. S. Ohadian Moghadam. A Review on Currently Available Potential Therapeutic Options for COVID-19. *Int. J. Gen. Med.* **2020**, Volume 13, 443–467.
75. Y. Wang, W. Jiang, Q. He, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: Single-center experience from Wuhan, China. *medRxiv* **2020**.
76. L. Zha, S. Li, L. Pan, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (<scp>COVID</scp> -19). *Med. J. Aust.* **2020**, 212 (9), 416–420.
77. Y. Ling, S.B. Xu, Y.X. Lin, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin. Med. J. (Engl).* **2020**, 133 (9), 1039–1043.
78. P. Mehta, D.F. McAuley, M. Brown, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **2020**, 395 (10229), 1033–1034.
79. Y. Song, M. Zhang, L. Yin, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). *Int. J. Antimicrob. Agents* **2020**, 56 (2), 106080.
80. J.A. Hippensteel, W.B. LaRiviere, J.F. Colbert, C.J. Langouët-Astrié, E.P. Schmidt. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am. J. Physiol. Cell. Mol. Physiol.* **2020**, 319 (2), L211–L217.
81. C. Conzelmann, J.A. Müller, L. Perkhofer, et al. Inhaled and systemic heparin as a repurposed direct antiviral drug for prevention and treatment of COVID-19. *Clin. Med. J. R. Coll. Physicians London* **2020**, 20 (6), 218–221.
82. C. Shi, W. Tingting, J.-P. Li, et al. Comprehensive Landscape of Heparin Therapy for COVID-19. *Carbohydr. Polym.* **2021**, 254 (January), 117232.
83. G. Cassinelli, A. Naggi. Old and new applications of non-anticoagulant heparin. *Int. J. Cardiol.* **2016**, 212, S14–S21.
84. C.M. Jackson. Mechanism of heparin action. *Baillieres. Clin. Haematol.* **1990**, 3 (3), 483–504.
85. L. Gozzo, P. Viale, L. Longo, D.C. Vitale, F. Drago. The Potential Role of Heparin in Patients With COVID-19: Beyond the Anticoagulant Effect. A Review. *Front. Pharmacol.* **2020**, 11 (August), 1–8.
86. C. Shi, C. Wang, H. Wang, et al. The Potential of Low Molecular Weight Heparin to Mitigate Cytokine Storm in Severe COVID-19 Patients: A Retrospective Cohort Study. *Clin. Transl. Sci.* **2020**, 13 (6), 1087–1095.
87. H. ten Cate. Surviving Covid-19 with Heparin? *N. Engl. J. Med.* **2021**, 385 (9), 845–846.
88. N. Tang, H. Bai, X. Chen, et al. Anticoagulant treatment is associated

with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J. Thromb. Haemost.* **2020**, 18 (5), 1094–1099.
89. B. Pajak, E. Siwiak, M. Sołtyka, et al. 2-Deoxy-d-Glucose and Its Analogs: From Diagnostic to Therapeutic Agents. *Int. J. Mol. Sci.* **2019**, 21 (1), 234.
90. R.L. Aft, F.W. Zhang, D. Gius. Evaluation of 2-deoxy-D-glucose as a chemotherapeutic agent: Mechanism of cell death. *Br. J. Cancer* **2002**, 87 (7), 805–812.
91. A. Narayan Bhatt, A. Kumar, Y. Rai, et al. Glycolytic inhibitor 2-Deoxy-D-glucose attenuates SARS-CoV-2 multiplication in host cells and weakens the infective potential of progeny virions. *bioRxiv* **2021**, 2021.06.12.448175.
92. D. Zhang, J. Li, F. Wang, et al. 2-Deoxy-D-glucose targeting of glucose metabolism in cancer cells as a potential therapy. *Cancer Lett.* **2014**, 355 (2), 176–183.
93. V. Malgotra, V. Sharma. 2-Deoxy-d-glucose inhibits replication of novel coronavirus (SARS-CoV-2) with adverse effects on host cell metabolism. **2021**, No. July, 1–20.
94. L. Horton, A.E. Torres, S. Narla, et al. Spectrum of virucidal activity from ultraviolet to infrared radiation. *Photochem. Photobiol. Sci.* **2020**, 19 (10), 1262–1270.
95. R. Kumar, K. Gulia, M.P. Chaudhary, M.A. Shah. SARS-CoV-2, influenza virus and nanoscale particles trapping, tracking and tackling using nanoaperture optical tweezers: A recent advances review. *J. Mater. Nanosci.* **2020**, 7 (2), 79–92.
96. B.S. Chhikara, R. Kumar, B. Rathi, S. Krishnamoorthy, A. Kumar. Prospects of Applied Nanomedicine: potential clinical and (bio)medical interventions via nanoscale research advances. *J. Mater. Nanosci.* **2016**, 3 (2), 50–56.
97. M. Heßling, P. Vatter. Ultraviolet irradiation doses for coronavirus inactivation – review and analysis of coronavirus photoinactivation studies Ultraviolette Bestrahlungsdosen für die Inaktivierung von Coronaviren. *GMS Hyg. Infect. Control* **2020**, 15, 1–8.
98. S.K. Bhardwaj, H. Singh, A. Deep, et al. UVC-based photoinactivation as an efficient tool to control the transmission of coronaviruses. *Science of the Total Environment.* 2021.
99. B.S. Chhikara, R. Kumar, Poonam, P. Bazard, R.S. Varma. Viral infection mitigations using advanced nanomaterials and tools: lessons from SARS-CoV-2 for future prospective interventions. *J. Mater. Nanosci.* **2021**, 8 (2), 64–82.
100. D. Welch, M. Buonanno, V. Grilj, et al. Far-UVC light: A new tool to control the spread of airborne-mediated microbial diseases. *Sci. Rep.* **2018**, 8 (1), 1–7.
101. M. Buonanno, D. Welch, I. Shuryak, D.J. Brenner. Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses. *Sci. Rep.* **2020**, 10 (1), 1–8.
102. F. Nicastro, G. Sironi, E. Antonello, et al. Solar UV-B/A radiation is highly effective in inactivating SARS-CoV-2. *Sci. Rep.* **2021**, 11 (1), 1–11.
103. A. Blanco, F. de B. Ojembarrena, B. Clavo, C. Negro. Ozone potential to fight against SAR-COV-2 pandemic: facts and research needs. *Environ. Sci. Pollut. Res.* **2021**, 28 (13), 16517–16531.

AUTHORS BIOGRAPHIES

Dr Kalpa Mandal is working as an Associate Professor in the Department of Chemistry of Dyal Singh College, University of Delhi. She did her PhD from Jai Narayan Vyas University, Jodhpur, Rajasthan, on Synthesis of polymeric complexing agents, their characterization by spectroscopic techniques and their applications in practical fields. Her research interests also include areas of Nanotechnology and Environmental chemistry. She has published many research papers and review articles in conference proceedings as well as National & International journals of repute. She has guided undergraduate students in innovation research projects. She has also authored two Books.

Dr. Meenakshi Singh is serving as Professor of Chemistry at Galgotias University, Greater Noida, India. Her research is focused on synthesis of Macrocyclic Complexes by using transition metals and characterization of such complexes by several spectroscopic techniques. She has long experience of teaching, research & administration. Her research interests are in Nanotechnology & ground water quality analysis by using various analytical & Spectroscopic techniques. She has been guiding M.Sc., B.Sc. students for their research projects since long. Students are also pursuing research under her supervision in field of Environmental Analytical Chemistry. She has been the member of various Committees at Galgotias University since 2012.

Dr Charu Chandra is an Assistant Professor in the Department of Chemistry, Dyal Singh College. University of Delhi. She received her Master's and Ph.D degree from University of Delhi. Her area of interest are Corrosion Chemistry and Environmental Chemistry with focus on research using Medicinal plants as Corrosion Inhibitors. She has published several research papers in reputed National and International Journals. She also undertook Innovation research projects funded by University of Delhi guiding undergraduate students.

Dr Indraj Kumar Kumawat is an Assistant Professor in the Department of Chemistry at Dyal Singh College, University of Delhi, India. He received his **Master's** degree from University of Rajasthan and **Ph.D.** degree from J N V University, Jodhpur, Rajasthan. His main research interests are in the areas of Organic Chemistry and Environmental Chemistry. His research is focused on synthesis, characterization, and application of polysaccharide-based resins. He has published several research papers in reputed international and national journals. He has also undertaken innovation research project funded by University of Delhi guiding undergraduate students.