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REVIEW ARTICLE

A Review on SARS CoV–2: History, Origin, Morphology, and the Predicted Strategy to Control the Pandemic through Metals and Metal–Based Compounds

Nabtahil Iqbal [1], Fawad Ahmad [1,*], Irum Jamil [1], Muhammad Imran Khan [2, *], Abdallah Shanableh [2,3], Aqsa Naz [4], Nosheen Farooq [5], Muhammad Babar Taj [4], Mushtaq Hussain Lashari [6], Suryyia Manzoor[7]

ABSTRACT: The epidemic of COVID-19, which threatened the mass, globally, was brought on by the newly discovered corona virus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The SARS-CoV-2 that caused COVID-19 has posed serious risks to people's health, public safety and the world's economy. Worldwide, considerable and quick research on pharmacological therapy is being conducted as a result of the COVID-19 pandemic. The particular characteristics of the metal centers now employed in medicinal chemistry make metallodrugs a good candidate for achieving the treatment objective. Here two key approaches are discussed for creating metal-based medicines that successfully combat SARS-CoV-2. A "Drug Repurposing" strategy and a "Discovery Approach" motivated by a pathway and based on prior knowledge may help. Selectivity and toxicity problems need to be taken into consideration while using metal compounds. Metal-related medications have long been used as antiviral medications and enzyme inhibitors, offering possible treatments for COVID-19. These display a broad range of bioactivities, showcasing incomparable advantages in pharmacology. For the SARS-CoV-2 infection, it is well established that metallodrugs play a significant role in direct antiviral therapy or in the inhibition of essential viral replication-related enzymes. They can also be used as vaccine adjuvant or as pharmaceuticals to boost the effectiveness of antiviral medications (like zinc with hydroxychloroquine). The rapid and persistent contributions of researchers from around the world during the spread of COVID-19 have led to numerous successful treatments. Several antiviral medications, anti-inflammatory medications, antibodies, corticosteroids and convalescent plasmas have been suggested for the treatment of COVID-19, thus far, although truly effective medications are still being tested. The purpose of this review is to give an overview of current developments in metal pharmacology-based COVID-19 therapy methods and the brief introduction to the usage of metal and metal-based medications currently and in the future.

Keywords: Virus, SARS-CoV-2, Metallo-drugs, Vaccine, Drug repurposing, Discovery strategy, Virtual screening.

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[1] Department of Chemistry, University of Wah, Quaid Avenue, Wah Cantt Postal Code 47040, Pakistan.
[2] Research Institute of Sciences and Engineering (RISE), University of Sharjah, Sharjah 27272, United Arab Emirates.
[3] Scientific Research Center, Australian University, Kuwait.
[4] Institute of Chemistry, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan.
[5] Department of Chemistry, The Government Sadiq College Women University, Bahawalpur-63100, Pakistan.
[6] Department of Zoology, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan.
[7] Institute of Chemical Sciences, Bahauddin Zakariya University, Multan, Pakistan

*Author to whom correspondence should be addressed:
raoimranishaq@gmail.com (Muhammad Imran Khan)

1. INTRODUCTION

Wuhan City Hubei Province, China, [1] (a city in central China with 11 million residents), [2] has had an outbreak of "pneumonia of unclear cause" since December 2019 [3]. The cause of the infection was ultimately determined to be the 2019 new coronavirus, also called SARS-CoV-2 which was then isolated and sequenced. Since then, SARS-CoV-2 has spread globally and is the cause of devastating sickness Coronavirus Disease 2019 (COVID-19). Medical laboratories have been creating several protocols to help diagnose SARS-CoV-2 and treat COVID-19 patients ever since the outbreak started [1]. The virus had spread worldwide despite significant efforts to restrict the illness in China, and COVID-19 was declared to be a pandemic by World Health Organization (WHO) in March 2020 [3]. Figure 1 clearly summarizes all the important incidents occurred since the spread of the virus until it was declared as a pandemic. Exposures at a fish market in Wuhan were connected to the initial cases. Figure 2 below displays the continuation of the virus from the expected source i.e. bats to the humans). The Chinese government recorded 2835 confirmed cases in mainland China as of January 27, 2020, including 81 fatalities, 39 foreign cases were found in Japan, South Korea, Thailand, France, Singapore, Canada, the United States, Nepal, Australia and Vietnam, in addition to 19 verified cases in Macao, Taiwan and Hong Kong. 2019-nCoV, a novel corona virus, which is closely linked to the CoV that results in SARS, was quickly identified as the pathogen. There isn't a particular medication for the new infection yet. Finding powerful antiviral medications to fight the disease is thus critically needed [3-10].

A typical laboratory approach for identifying respiratory viral pathogen, such as influenza and Respiratory Syncytial Virus (RSV), is a Reverse Transcription Polymerase Chain Reaction (RT-PCR). At the moment, it is the primary test type for the identification of SARS-CoV-2 infection in patients. RT-PCR is a reliable method for detecting RNA, while amplifies Complementary DNA (cDNA) targets specific to the pathogen of interest once/while reverse transcribed RNA is converted into cDNA.

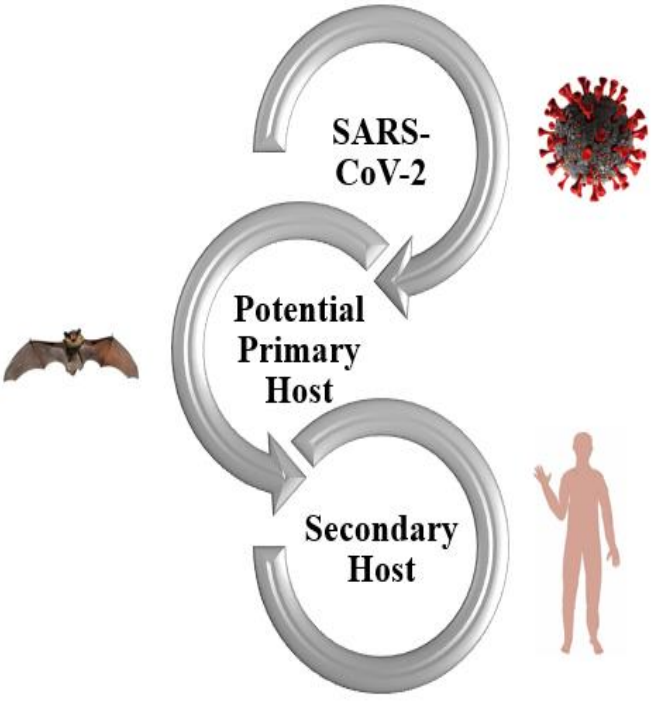

Fig. 2. Overview of COVID-19 progression.

This assay will identify SARS-CoV-2 RNA if it is found in patient specimen, commonly obtained as a Nasopharyngeal (NP) or Anterior Nasal Swab, as shown below in Figure 3. Once the specimen has arrived in the lab and has been transferred to the platform, these tests can be finished in less than an hour to many hours, depending on the platform [1].

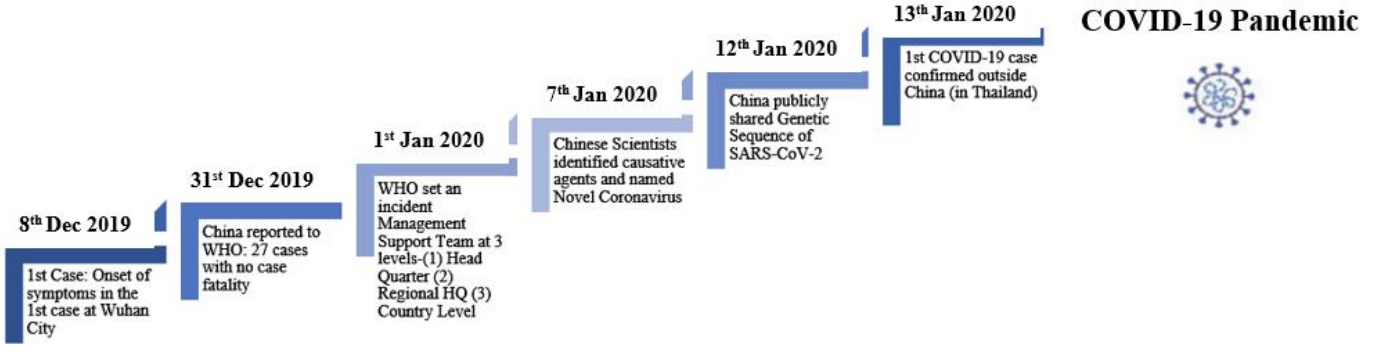

Fig. 1. The main historical occurrences in the SARS-CoV-2 outbreak. Reprinted with the permission from ref. [4] Kumar, A., Singh, R., Kaur, J., Pandey, S., Sharma, V., Thakur, L., Sati, S., Mani, S., Asthana, S., Sharma, T.K. and Chaudhuri, S. **2021**. 'Wuhan to world: the COVID-19 pandemic', *Frontiers in Cellular and Infection Microbiology*, 11, pp.596201. Copyright @ Frontiers.

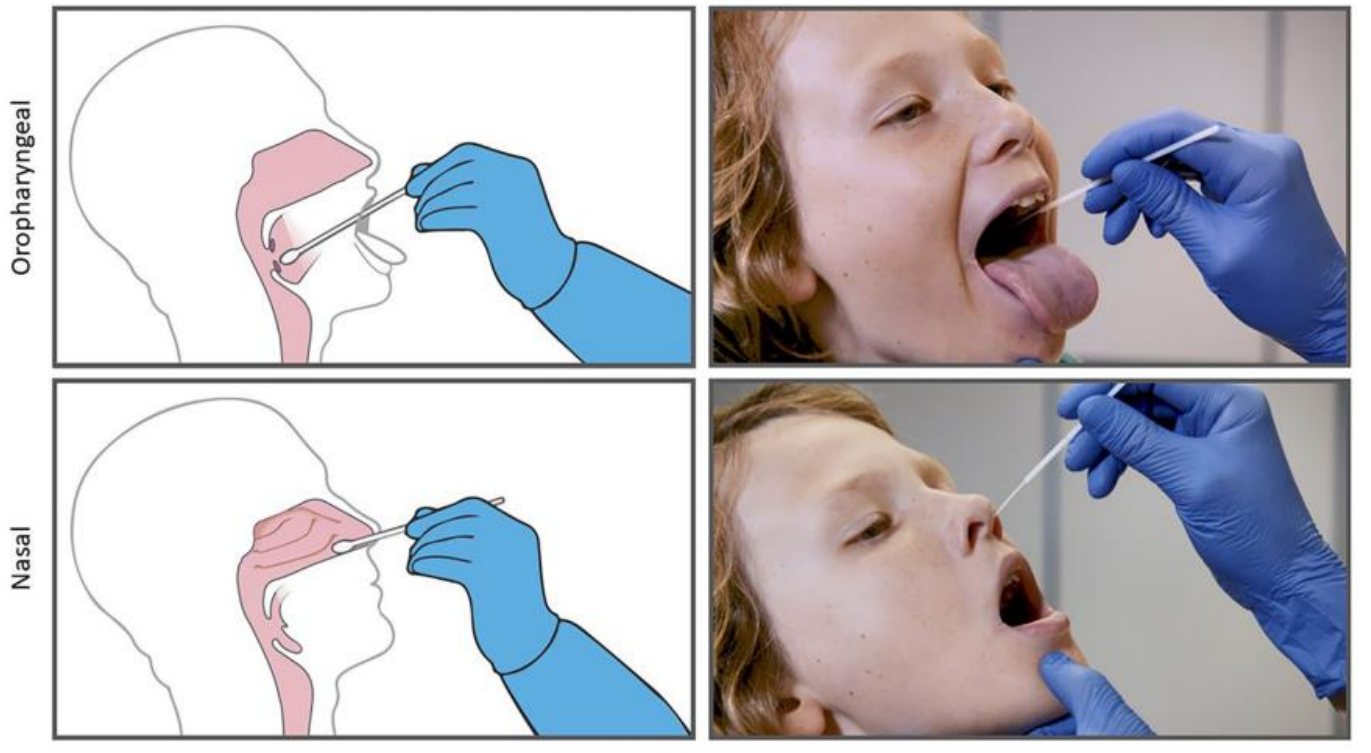

Fig. 3. Anterior nasal/ oropharyngeal swab for COVID-19 identification test. Reprinted with the permission from ref. [5] Mullane, M.J., Thomas, H.M., Epstein, M., Mandzufas, J., Mullan, N., Whelan, A., Lombardi, K., Barrow, T., Ang, S., Leahy, A. and Cameron, E. **2021**. 'Detect schools study protocol: a prospective observational cohort surveillance study investigating the impact of COVID-19 in Western Australian schools', *Frontiers in Public Health*, 9, pp.636921. Copyright @ Frontiers.

1.1. Morphology of the virus

Right now, COVID-19 is wreaking havoc on human health and the global economy. It is a single stranded positive-RNA virus that is transmitted via viral droplet inhalation. The genome generates four structural proteins: Spike protein (S), Membrane protein (M), Envelope protein (E) and Nucleocapsid protein (N) as depicted below in Figure 4. The corona virus capsid consists of a protein shell containing a positive strand of RNA that allows the virus to regulate the machinery of human cells. It has various varieties, including SARS and MERS and a new variant reported in 2019 that is a novel corona virus which causes unique COVID-19. A PCR-based test was used in the clinic to determine the existence of the virus [6].

1.2. Background of Coronavirus

CoV is present in a wide range of animal species, including humans. They are members of the Orthocoronaviridae subfamily (order: Nidovirales, subordination: Cornidovirineae, family: Coronaviridae). There are four genera of CoV, including α-/β-/γ- and δ-CoV. α- and β-CoV can harm animals, whereas γ- and δ-CoV primarily infect birds. CoV are encapsulated viruses with viral surface proteins contained in a lipid membrane produced from the host cell. The name "corona" (Latin: Garland, Crown) comes from the proteins that protrude from the membrane of the virus, particularly the (S) protein, which gives these viruses their distinctive halo-like appearance when observed under electron microscope.

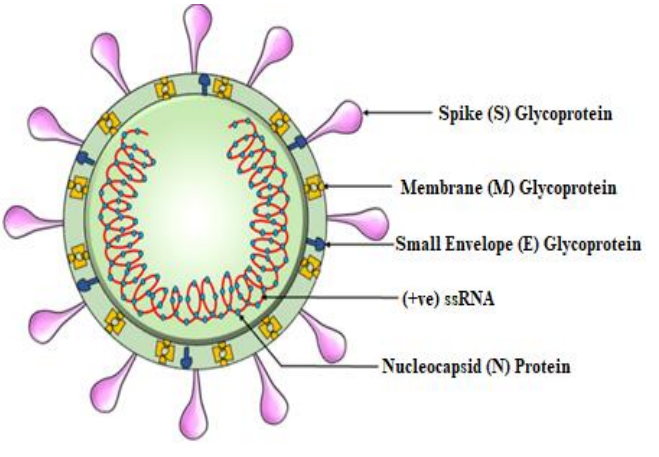

Fig. 4. The corona virus structure is depicted schematically. Reprinted with the permission from ref. [7] Shah, V.K., Firmal, P., Alam, A., Ganguly, D. and Chattopadhyay, S. **2020**. 'Overview of immune response during SARS-CoV-2 infection: lessons from the past', *Frontiers in Immunology*, 11, pp.1949. Copyright @ Frontiers.

All CoV share the property that their genomes are composed of a single-stranded RNA with positive polarity which means that the RNA's base sequences are oriented (5′→3′) in a manner that is similar to the later messenger RNA (mRNA). The CoV genome is known to be the largest existing RNA, measuring 26.4-31.7 kilobases. The viral RNA encodes four crucial structural proteins, including the (N) protein that surrounds the RNA genome and three membrane proteins, the (S)-glycoprotein, the (M) protein and the (E) protein, in addition to a number of nonstructural proteins like the RNA-dependent RNA polymerase (RdRp) [3]. RdRp is a crucial protease for corona virus that catalysis RNA replication from an RNA template and is a desirable therapeutic target [8].

The Infectious Bronchitis Virus (IBV), the first corona virus to be identified, was discovered in chicken embryos in 1937. Since, then a variety of CoV have been found in a wide range of species, such as agricultural animals, pets and wild animals. The bird associated γ- and δ-CoV and mammalian associated α- and β-CoV have different genera [3].

1.3. Severity of the Virus

Animals can develop sickness from corona virus infections that might range from mild to severe respiratory, intestinal or systemic. There is a lot of infection in animals due to corona virus, though that doesn't seem to develop any symptoms. The fact that CoV is present in so many different animal species firmly suggests that these viruses are zoonotic in nature and spread in humans from wild animals. The epidemic of SARS in 2002-2003 in particular has prompted an increase in research on wild animals across all continents. The majority of CoV diversity has far been found in bats. As a result, it has been proposed that atleast some of the more recent CoV introductions to human were first bat viruses that transmitted to an intermediate animal, such as the Himalayan Palm-Civet for SARS-CoV and the Dromedary Camel for Middle East Respiratory Syndrome Corona Virus (MERS-CoV), which subsequently exposed humans to the viruses. It is likely that there are still significant gaps in the knowledge of zoonotic CoV in populations of wild animals. Particularly, incomplete statistics exist for regions of the world that are economically and/or politically unstable [3].

1.4. Coronavirus in Humans

The earliest Human Corona Viruses (HCoV) were identified as HCoV-229E and HC0V-OC43 in the 1960s. Currently, 4 endemic HoCVs (HoCV-229E, HoCV-OC43, HoCV-NL63 and HoCV-HKU1) are known circulating in the global human population. Most of the time, these endemic HoCVs result in relatively minor infections of the upper and lower respiratory tract, and it is thought that they are responsible for around one-third of all human "common colds". Infections without symptoms have also been reported. Acute respiratory failure can also develop in some circumstances, particularly in immunosuppressed people, kids or people who already have pulmonary illnesses. The emergence of the SARS-CoV significantly altered the scenario. In China between 2002 and 2003, this virus led to significant respiratory illnesses in people. At that time, the disease infected about 8000 individuals, with a mortality rate of about 9.5%. The quick development of a detection technique and extensive isolation measures for affected people could stem the spread of the SARS-CoV [3]. Figure 5 displays human attacking sites by the virus as well as some common initial symptoms.

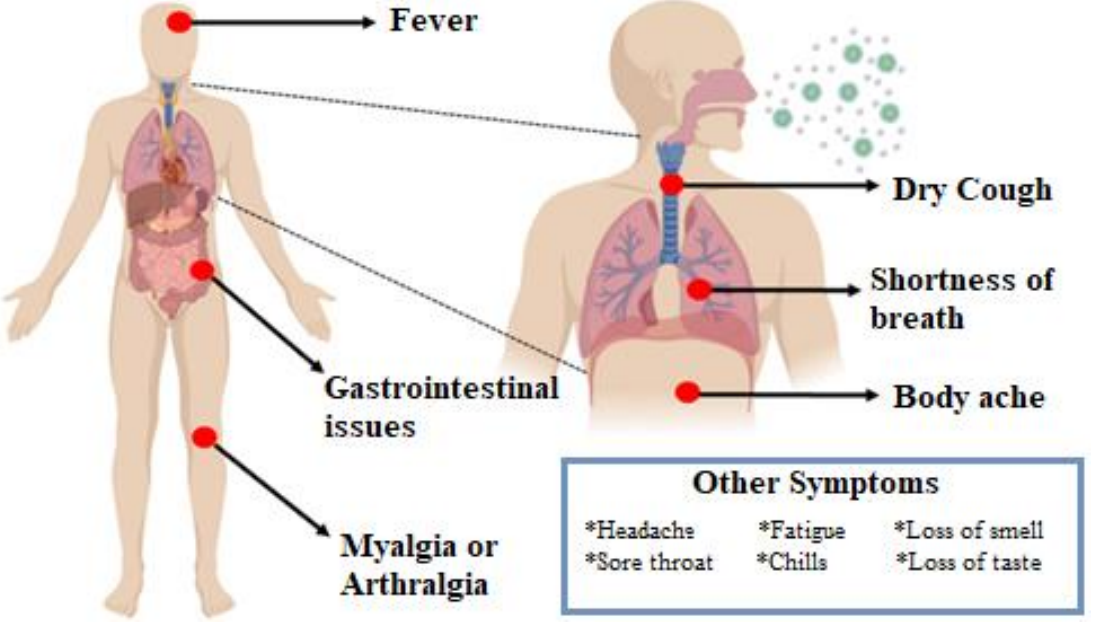

Fig. 5. COVID-19 symptoms. Reprinted with permission from ref. [9] da Silva, S.J.R., Silva, C.T.A.D., Guarines, K.M., Mendes, R.P.G., Pardee, K., Kohl, A. and Pena, L. **2020**. 'Clinical and laboratory diagnosis of SARS-CoV-2, the virus causing COVID-19', *ACS Infectious Diseases*, 6(9), pp.2319-2336. Copyright @ ACS Publications.

2. SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS2 (SARS-COV-2)

In 2019, end of December, China reported a spike in pneumonia cases in Wuhan (Hubei). The WHO designated the virus-caused illness COVID-19 and the International Committee for Taxonomy of Virus (ICTV) gave the virus its official designation of SARS-CoV as further data and genetic analysis became available [3]. The novel corona virus DNA shares similarities with existing β-CoV identified in bats. SARS-CoV-2 shares 79.5% similarity with SARS-CoV [10] while being 96.2 % comparable to a bat CoV named RaTG13. Therefore, it can be inferred that the virus originated in bats and spread through time to various animal hosts before eventually infecting people as shown below in Figure 6. The divergence of two common SARS-CoV-2 evolution types, L type (70%) and S type (30%), was documented, despite the fact that SARS-CoV-2 has less diversity than, for instance, influenza viruses. The study shows that L type strains, which are descended/ evolved/ generated from S type, have evolved to be more aggressive and contagious. The use of "Angiotensin-Converting Enzyme 2" (ACE2) as a cellular receptor by SARS-CoV-2 to infect people is now known to have occurred. In our globalized environment, SARS-CoV-2 effectively transmitted from person to person and has therefore able to spread quickly across the world. 601,478 persons have caught/ infected COVID-19 as a result, and 27,961 sufferers have passed away (as of March 28, 2020, source: John Hopkins University) [3].

2.1. Effects of Coronavirus Infection on Intensivists and Anesthesiologists

Anesthesiologists and intensivists are particularly vulnerable to exposure to the novel corona virus due to their work with COVID-19 patients and regular use of techniques that produce aerosol (such as nebulized therapies, open suctioning and endotracheal intubation). Comparatively speaking to the general population, health care employees have higher chances of getting an infection by the pathways mentioned below in Figure 7. Additionally, because anesthesiologists and intensivists deal for these patients, it is important for them to have a basic understanding of COVID-19 and SARS-CoV-2 in order to manage these patients and protect themselves in the best way possible [3, 11].

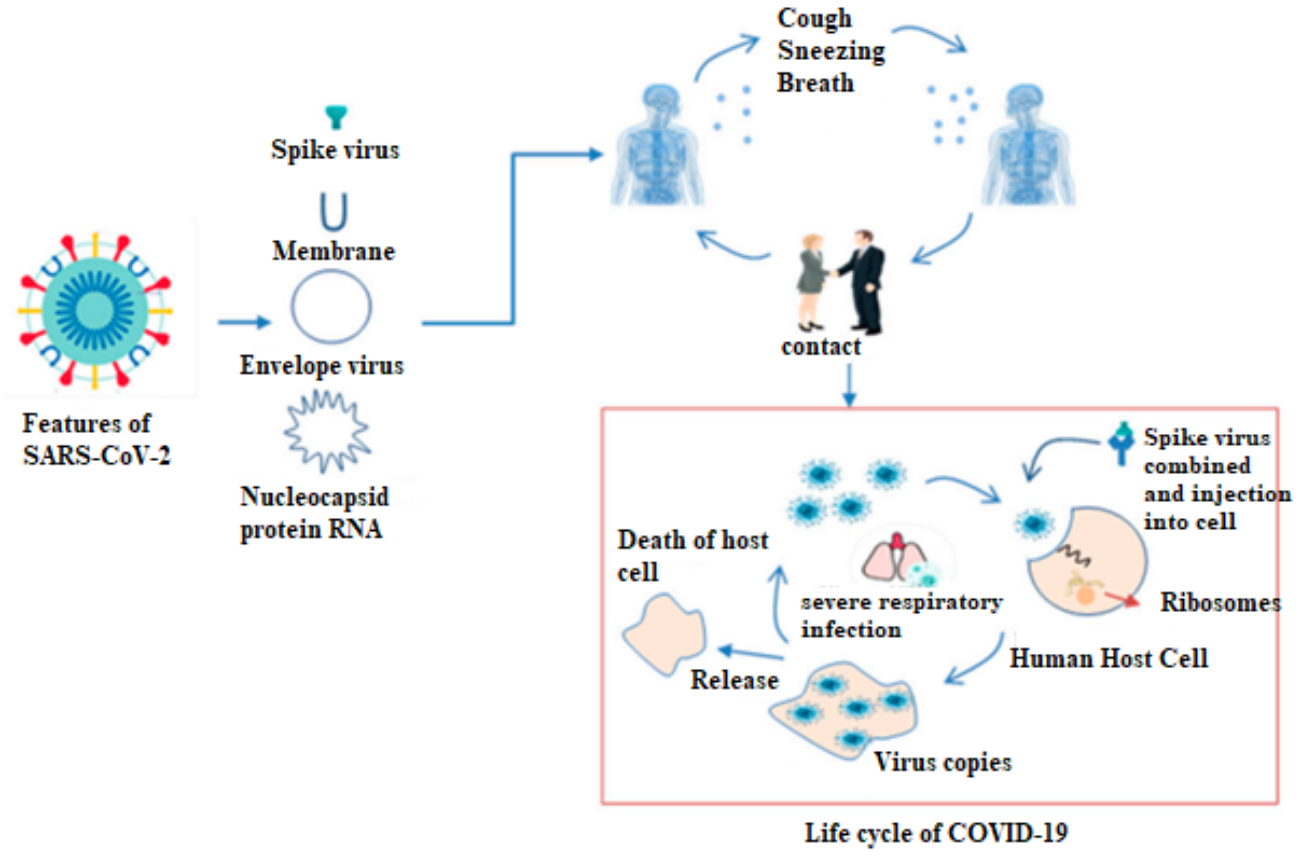

Fig. 6. Transportation of COVID-19 to human lungs. Reprinted with the permission from ref. [11] Taha, B.A., Al Mashhadany, Y., Bachok, N.N., Ashrif A Bakar, A., Hafiz Mokhtar, M.H., Dzulkefly Bin Zan, M.S. and Arsad, N. **2021**. 'Detection of COVID-19 virus on surfaces using photonics: challenges and perspectives', *Diagnostics*, 11(6), pp.1119. Copyright @ MDPI.

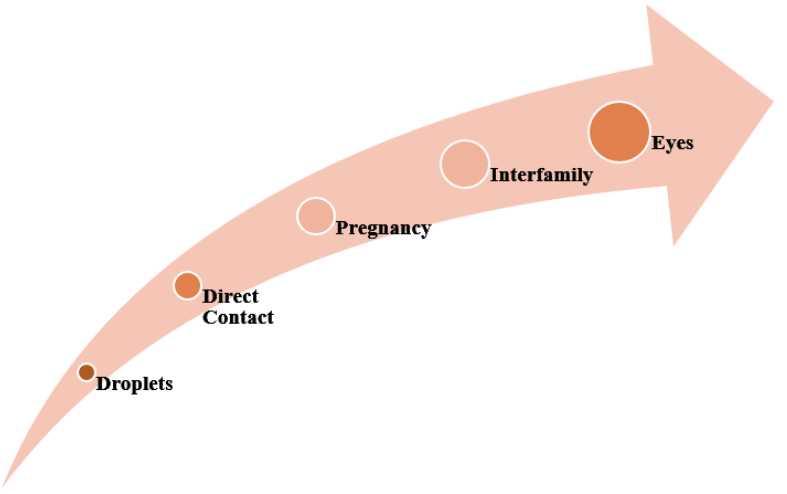

Fig. 7. Pathways of COVID-19 virus dispersal from human to human.

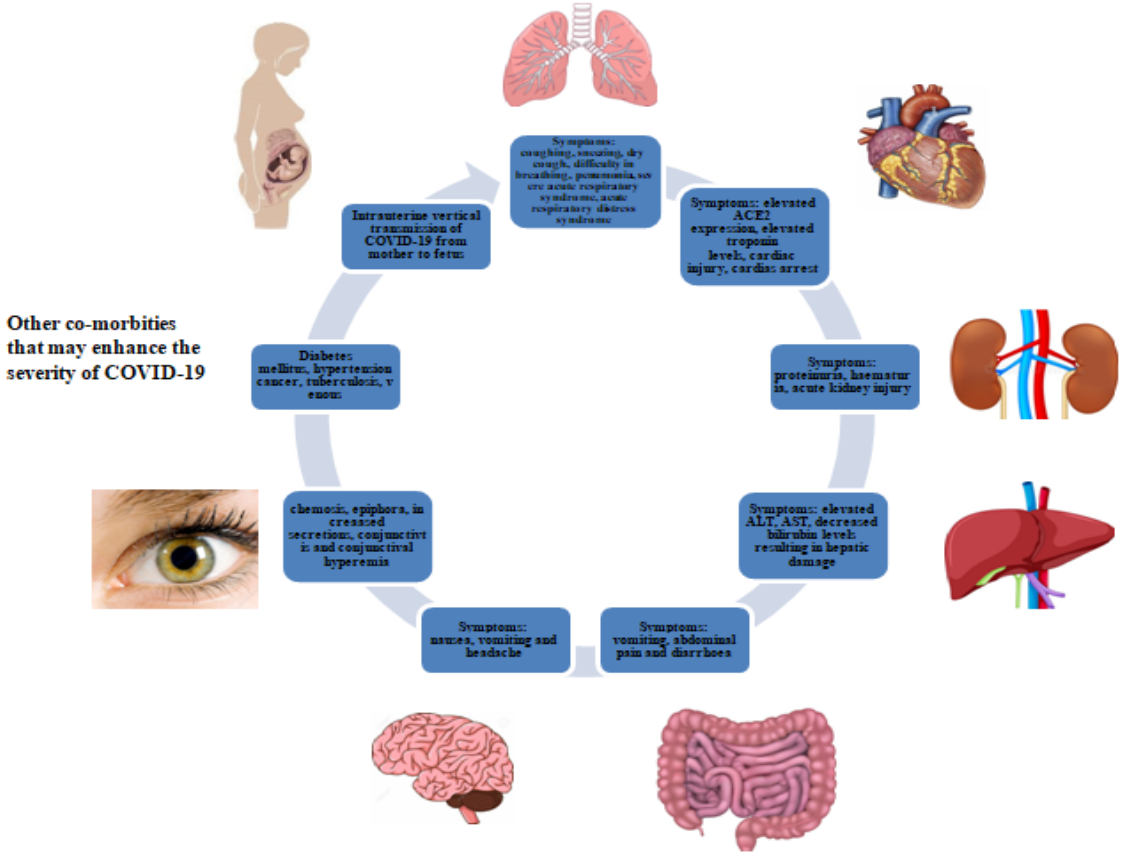

Fig. 8. SARS-CoV-2 symptoms in healthy individuals and those who have additional co-occurring diseases. Reprinted with permission from ref. [12] Renu, K., Prasanna, P.L. and Gopalakrishnan, A.V. **2020**. 'Coronaviruses pathogenesis, comorbidities and multi-organ damage-A review', *Life Sciences*, 255, pp.117839. Copyright @ Elsevier.

2.2. Some Common Symptoms of SARS-CoV19

Dry cough, sneezing and breathing difficulties are among the characteristic signs and symptoms of SARS-CoV-2. The severity is influenced by a person's age, immunity a number and of co-morbid illnesses, including cancer, tuberculosis, diabetes mellitus, hypertension, heart problems and venous thromboembolism. After contacting SARS-CoV-2, the patient's pre-existing co-morbid conditions get worse. Figure 8 shows some of the most common symptoms caused by

COVID-19 in healthy people as well as patients with co-morbid conditions. Acute kidney injury, proteinuria and hematuria in the kidney, elevated Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST) levels indicating liver damage, conjunctivitis and conjunctival hyperemia in the eye, intrauterine transmission of the SARA-CoV-2 from mother to foetus, vomiting and diarrhea are some of the additional effects of the SARS-CoV-2 on various organs [12].

2.3. Life Cycle of the SARS-CoV-2 virus and Possible Nanomaterial Targets

The entire genome has been sequenced [13, 14], and it has significant gene similarities to other coronaviruses that are responsible for causing respiratory illness like SARS-CoV [14, 15]. Based on the information acquired during the SARS-CoV outbreak, the ACE2 surface receptor in human cells, that is found to be necessary for effective uptake in host cells, is one of the virus' primary target [13, 14, 16-18].

ACE2 receptors on the surface of the host cell are where SARS-CoV-2 interacts. Through its protease activity, Transmembrane Serine Protease 2 (TMPRSS2) enables the entry in the cell. Virus particles eventually internalize and enter endosomes. Uncoated viral particles release the viral DNA for protein synthesis as a result of low endosomal pH. Viral RNA and protein production is followed by the assembly and release of new infectious particles [14].

SARS-C-terminal CoV-2's region, which is also known as the receptor-binding domain of the envelope-embedded (S) protein, binds ACE2. The complex's crystal structure has been solved, revealing the chemical specifics of this interaction [14, 19]. The majority of therapy strategies target preventing the (S) protein from binding to ACE2, which is essential for the initial infection stages. Currently, there are three basic methods for preventing ACE2 binding:

I. Injection of a soluble, recombinant ACE2, a decoy receptor that scavenges the virus and prevents entry into host cells [14, 16];
II. Vaccination with specialized (S) protein-binding antibodies that blocks ACE2 interaction; and
III. Suppression of host proteases, which are involved in the processing of the (S) protein and are necessary for binding the ACE2 and subsequent membrane fusion allow intracellular viral transmission [14, 18].

The contacts between the target cells expressing ACE2 and the virus, as seen in Figure 9, are the initial infection events that are now being understood at the molecular level. However, due to the fact that patients with severe symptoms, which typically do not appear for several days or a week, already have a high viral load in their lungs, it is urgent to develop methods that will not only stop host cells from becoming infected but will also target persistent viruses that have previously been there and stop potentially fatal processes like lung hyperinflammation and multiple organ failure [14, 20]. Interestingly, a thorough Protein-Protein Interaction (PPI) map of the majority of viral proteins with the human proteome has been created to offer relatively novel targets for therapy using already FDA-approved medications in a procedure known as drug repurposing [14, 21].

2.4. The Clinical Picture

The primary means of the spread of COVID-19 are respiratory droplets, respiratory secretions and direct contact. The isolation of SARS-CoV-2 from blood and faecal swabs has also been reported, suggesting that there may be numerous routes of transmission. But this requires more explanation. The available data points to an incubation period of 1-14 days, with 3-7 days being the norm. The virus is extremely contagious in people and poses serious health risks, particularly to the elderly and those with underlying chronic illnesses. COVID-19 patients frequently exhibit distinct, comparable symptoms such as malaise, fever and cough. Most SARS-CoV-2 infected adults or kids have mild flu-like symptoms when they first become ill, but a small number of patients quickly deteriorate into crucial state and experience Acute Respiratory Distress Syndrome (ARDS), respiratory failure, multiple organ failure and even death. The most frequent clinical signs of COVID-19, according to a recent study, were fever (88.7%), cough (67.8%), exhaustion (38.1%), and sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%) and headache (13.6%). Only a few patients experienced gastrointestinal problems, including vomiting (5.0%) and diarrhea (3.8%). Upper respiratory symptoms and gastrointestinal problems were uncommon, whereas fever and cough predominated. The case fatality rate rises with illness severity and can reach upto 49% in patients who are extremely ill. Currently, only preventive actions can be used [3].

2.5. Searching for Drugs to Combat COVID-19

For COVID-19, no particular antiviral therapy is advised. New drug licensing and increasing usage guidelines for medicinal products that are already approved for use in treating additional conditions would be the most promising remedies in the near future. The anti-HIV drug; Lopinavir/Ritonavir, the antimalarial medications; Chloroquine and Hydroxychloroquine and Remdesivir (GS5734), an inhibitor of RNA Polymerase having in vitro action against numerous RNA viruses including Ebola, are just a few of the therapeutic candidates that have been proposed and evaluated. The outcomes of many of these initial experiments, however, are compromised by their small sample size and or poor non-rigorous study designs. No benefit was seen above and beyond conventional therapy when Lopinavir/ Ritonavir was tried in a rigorous, randomized, controlled, open-label trial comprising hospitalized adult patients with proven infection of SARS-CoV-2.

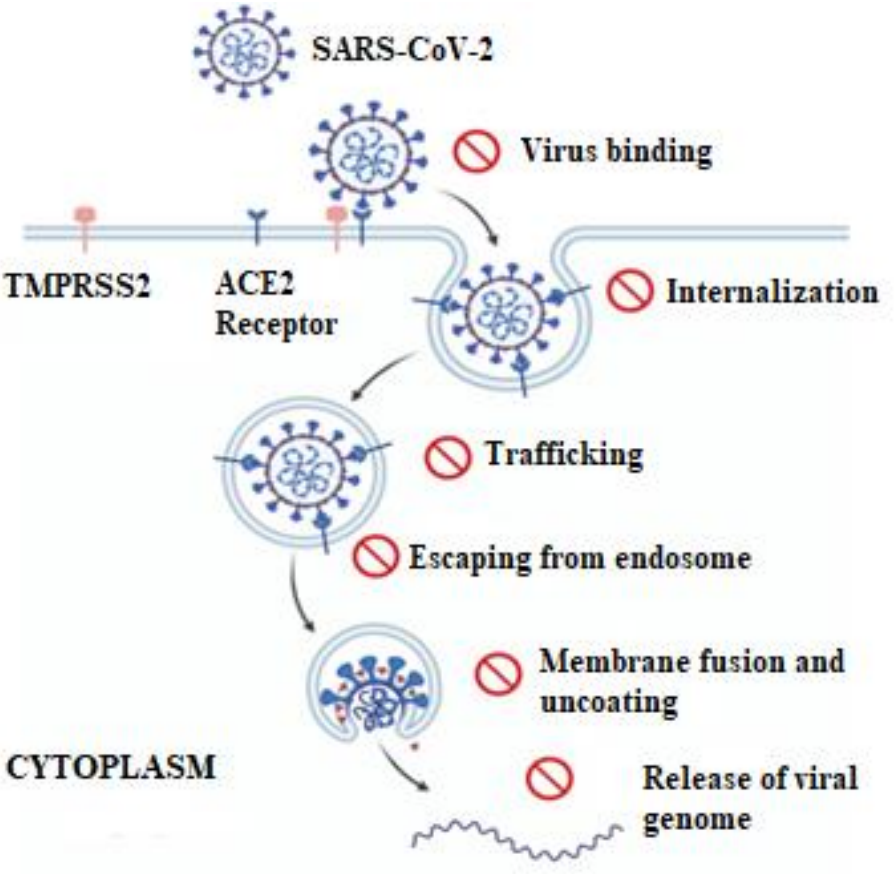

Fig. 9. Attacking Procedure of SARS-Covid-19. Reprinted with the permission from ref. [14] Weiss, C., Carriere, M., Fusco, L., Capua, I., Regla-Nava, J.A., Pasquali, M., Scott, J.A., Vitale, F., Unal, M.A., Mattevi, C. and Bedognetti, D. **2020**. Toward nanotechnology-enabled approaches against the COVID-19 pandemic. *ACS nano*, 14(6), pp.6383-6406. Copyright @ ACS Publications.

Despite the fact that using hydroxychloroquine in a more recent trial, encouraged and demonstrated that treatment is strongly linked to a decrease or disappearance of the viral load in COVID-19 patients, this study only included a small number of participants and is therefore thought to have very limited validity [6]. Similar to the existing dearth of reliable, thorough clinical investigations, numerous clinical trials have been initiated globally. As an illustration, Europe has started extensive cooperative clinical research of novel medications to treat COVID-19 [3].

a. Remdesivir

In cultured cells, NonHuman Primate (NHP) and mice, Remdesivir (GS5734) Fig. 10, has recently been identified as a potential antiviral medication against a wide range of RNA viruses, including SARS/ MERS-CoV infection. It is currently being developed clinically to treat Ebola virus infection. It is given via injection into a vein. Remdesivir was permitted or approved for usage in many nations during the COVID-19 epidemic to treat it [2]. Numerous hospitals are currently participating in the clinical trial, and efficacy testing its forthcoming [6]. Remdesivir, according to preclinical studies, may be useful for treating and preventing HCoV infections [3]. This nucleotide analogue, has lately gained attention as a possible anti-viral treatment since it works in pre-clinical studies [4, 22, 23] on RNA viruses like SARS/ MERS-CoV at the post-viral entry stages and enhances the pre-mature termination [4, 24].

b. Chloroquine

Recently, it was revealed that frequently prescribed anti-malarial drug Chloroquine (Figure 11), a medication for autoimmune disorders, may also be a possible broad-spectrum antiviral medication [2]. It is an anti-malarial and anti-autoimmune medication, which has just been recognized as a potential broad-spectrum antiviral drug [4, 25]. It works by raising endosomal pH, which is necessary for virus/ cell fusion and by preventing the viral receptors' glycosylation process [4, 26-35], thus, preventing viral spread and infection. Chloroquine worked to treat the 2019-nCoV infection in Vero E6 cells at both the entry and post entry stages [34, 16]. In addition to having antiviral properties, chloroquine also has

immune-modulating properties that may act together to increase its antiviral impact in vivo [4, 22]. Chloroquine has been tested in a variety of randomised controlled trials to see if it can be used to treat COVID-19. Fever control, improved CT imaging and a halt in disease development have all been benefits of therapy [6]. It has been shown that pairing remdesivir and chloroquine efficiently suppresses COVID-19 in vitro [4, 22].

c. Hydroxychloroquine

The antiviral effects of hydroxychloroquine (Figure 12) are quite comparable to those of chloroquine. Both have immune modifying properties that could improve their in vivo antiviral effectiveness. According to a Forbes article from March 30th, 2020 the use of chloroquine and hydroxychloroquine for the treatment of corona virus has received FDA approval in an emergency situation [6].

d. Theaflavin

It has been found to have antiviral action against a number of viruses, including influenza A, B and C. Theaflavin (Figure 13) was identified by Wiener to be a potential lead chemical for the creation of an inhibitor for 2019-nCoV [6].

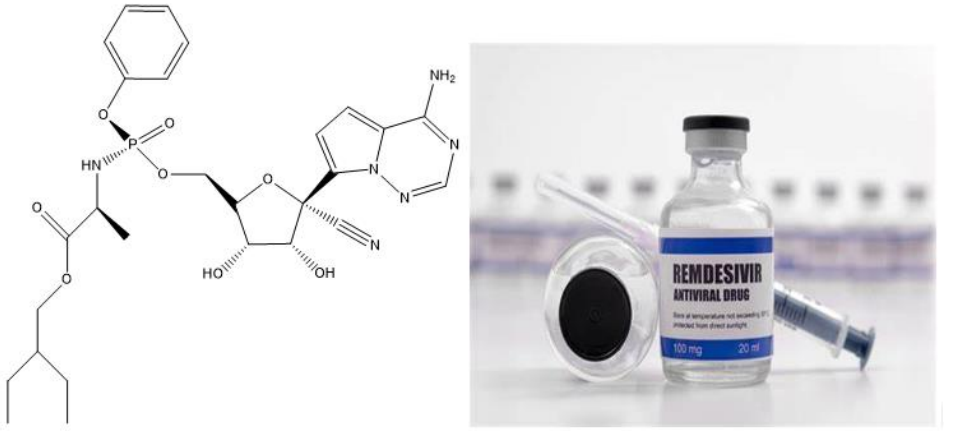

Fig. 10. Structure of Remdesivir.

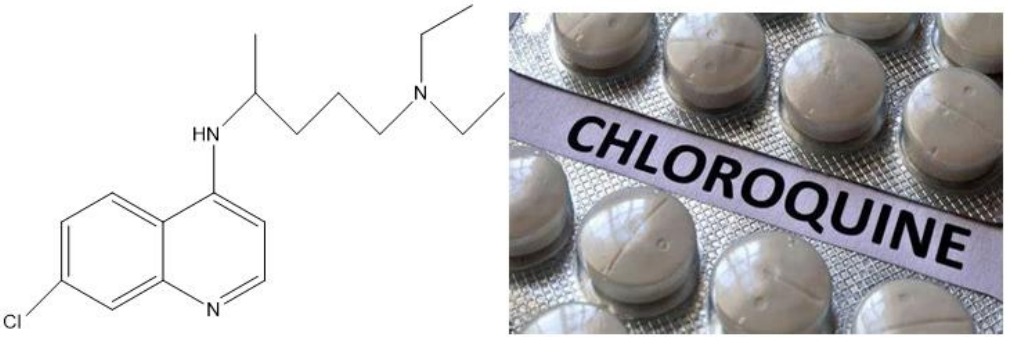

Fig. 11. Structure of chloroquine.

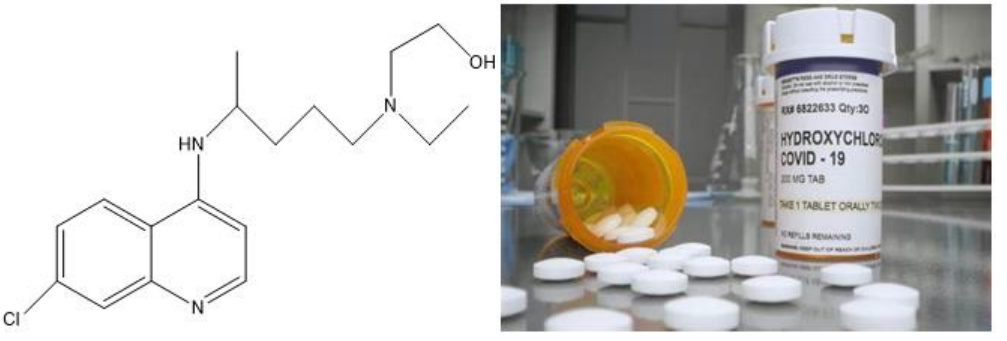

Fig. 12. Structure of hydroxychloroquine.

Fig. 13. Structure of Theaflavin.

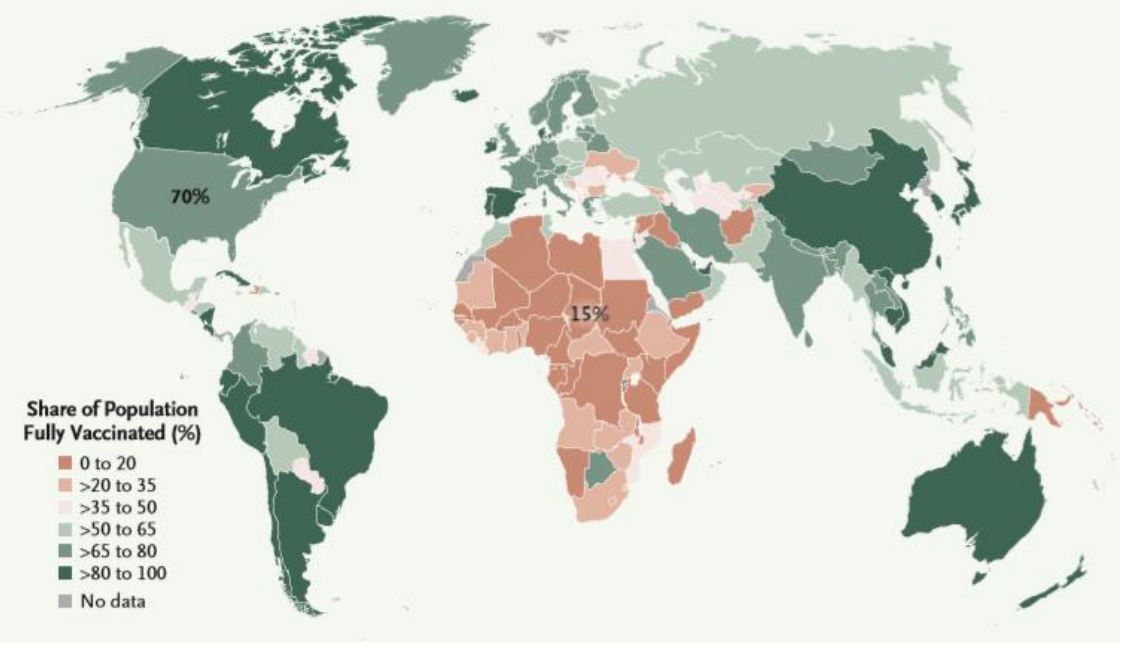

Fig. 14. Percentage of fully vaccinated people till July 8, 2022. Reprinted with the permission from ref. [27] Barouch, D.H. **2022**. 'Franklin H. Epstein Lecture: Covid-19 Vaccines-Immunity, Variants, Boosters', *The New England Journal of Medicine*. Copyright @ Massachusetts Medical Society.

According to the survey, remdesivir and chloroquine are very helpful at preventing in vitro infection of Covid-19. These substances are recommended to be tested in people with the novel corona virus disease since they have already been successfully used in human patients with a history of safety and have been found to be beneficial against a variety of illnesses [2]. Figure 14 below represents the data of the percentage of people vaccinated in different parts of the world.

2.6. Strategies to treat

The pandemic of COVID-19 presents a distinct challenge for the quick development of medications to treat this fatal illness. Because of the unusual properties of the metal centers now utilized in medicinal chemistry, metallodrugs may present a fantastic opportunity to accomplish this objective.

Here are two key approaches for creating metal-based medicines that are efficient against SARS-CoV-2. First, a few metallodrugs with clinical approval might be tested on patients using a "Drug Repurposing" strategy. The gold medication "Auranofin" appears to be a potential possibility in this regard, but other clinically proven metal compounds are deserving of careful considerations. On the other hand, to find the most efficient molecules, libraries of inorganic compounds with a wide chemical variety should be screened. A pathway-driven discovery approach based on a general

understanding of the mechanism of action, which can be used to limit the functional activities of the main viral proteins, may help with the second option. Concerns with selectivity and toxicity must also be taken into account.

3. POSSIBILITIES FOR COVID-19 TREATMENT

The abrupt onset and global spread of COVID-19 provide serious challenges to the healthcare systems because there was unavailability of vaccine, medication or treatment that was actually effective. The best defense against viral diseases is unquestionably vaccination. There are, however, obvious risks associated with vaccination, for instance the potential for incomplete virus inactivation or adverse effects in people. Even after a vaccine has been developed, a highly precise quality control is necessary to ensure the safety of the treatment. As a result, developing a vaccination is an extremely drawn-out process; even years after the discovery of a novel pathogen, a vaccine may not be commercially available. Despite the enormous efforts put forth over the past few decades, no effective vaccine against HIV has yet been created; persons who are HIV infected today enjoy a good quality life because of the accessibility of numerous and potent anti-HIV medications. Similar to this, the global scientific community is working assiduously to create vaccines quickly against SARS-CoV-2 virus. Therefore, just like with HIV infection, it is crucial and urgent to find and quickly apply potent antiviral medications against SARS-CoV-2.

3.1. Attacking procedure

Consequently, the global scientific community is making great efforts to discover novel compounds that can combat the SARS-CoV-2 virus. In this regard, molecular level understanding of the virus is advancing quickly, and potential therapeutic targets are being found and defined. The SARS-CoV-2 virus's RNA genome sequence, which has already been identified, provides hints for choosing the primary targets and developing potent treatments. In fact, 4 structural and 25 nonstructural viral proteins totaling 29 unique proteins were found. It is noteworthy that SARS-CoV-2 has a (S) protein that is in charge of the virus's attachment to the ACE2 on the host cell's surface. After entering the cell, the viral RNA binds to the host ribosome to create two polyproteins necessary for the development of fresh mature virions. The corona virus major Proteinase (3CLpro) and the Papain (PLpro), two viral Cysteine Proteases, in turn carry out the proteolytic cleavage of these polyproteins. The RdRp, which is in charge of replicating the RNA genome, is also present in SARS-CoV-2. There are specific attempts being made to discover compounds that can hit these targets selectively since it is thought that all of the aforementioned proteins represent primary druggable targets to inhibit the growth and replication of SARS-CoV-2 [28, 36-49].

3.2. Effect of COVID-19 Vaccines on Pregnant Females

Long recognized are the advantages of maternal immunization for the child due to the placental transmissions of maternal antibodies. Babies born to moms who had gotten the smallpox vaccination in the 1870s were less likely to the contract the disease when they were young. American College of Obstetricians and Gynecologists have strongly recommended vaccination for pregnant females due to the increased risk of severe diseases and pregnancy associated with COVID-19. Figure 15 below shows the percentage of pregnant women in US who got the vaccination [29].

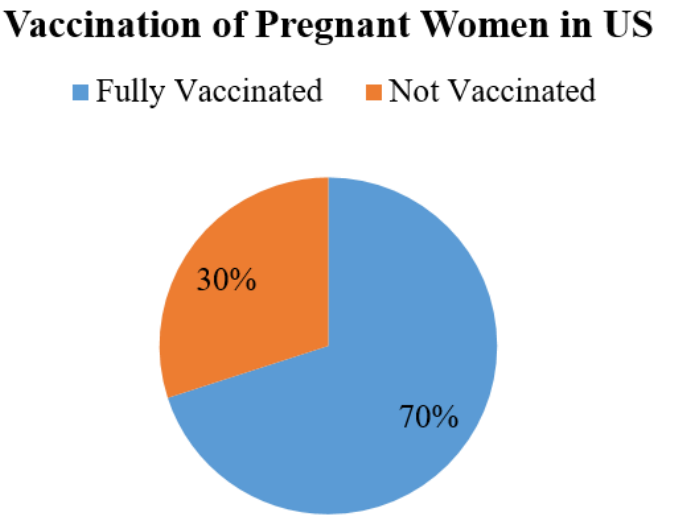

Fig. 15. Percentage of total vaccinated and non-vaccinated pregnant women in US.

3.3. Suggested Treatment Methods

"Drug repurposing", or using medications that are currently on the market for a different therapeutic purpose, is a simple method to identify active molecules that are easily accessible to the doctors to combat the COVID-19 condition. A significant amount of research is being done on FDA approved libraries of medications and a few intriguing candidates for drug repurposing against COVID-19 illness have already been found (e.g. Tocilizumab, Chloroquine, Remdesivir). It might surprise you to learn that currently no metal compound is undergoing clinical testing for this condition through repurposing. The testing of novel metal-based medications is also quite restricted at the moment. We think that thorough testing of metallodrugs as possible anti-COVID-19 medicines may present significant opportunity.

4. EFFECTS OF METAL BASED COMPOUNDS

By directly inhibiting enzymes, alterations of transcription factors, interacting through coordinative bonding with a

number of biomolecules, increasing lipophilicity, changing the functions of cell membranes, interfering with the cell cycle and other mechanisms, metal compounds are thought to have an impact on cellular and biological processes. The Pearson HSAB theory states that soft metal centers are typically present in medicinally used metal compounds, for example Au(I), Pt(II) or Ag(I), which is distinguished by a high affinity for enzymes and proteins with readily accessible thiol or selenol groups that have functional importance.

4.1. Toxicity of metal compounds

It is highly encouraged that the International Scientific Community investigates the potentialities of metal compounds in drug development programmes for COVID-19. As metal-based medications are frequently recognized to cause relevant negative effects, it is crucial to evaluate toxicity issues in this process. However, it is difficult to anticipate the toxicity of a metal complex because it vitally depends on both the nature of the metal center and the nature of its ligands. In fact, the safety statement must incorporate at least two different types of toxicity evaluation, acute and systemic toxicity for which a variety of in-vivo, in-vitro or even in-silico models and methodologies must be used.

4.2. Drug development by repurposing clinically proven metal based drugs

The repurposing of metal-based medications that have been clinically licensed for use in other therapeutic applications against the COVID-19 is, as was already said, a straightforward method for finding effective metallodrugs for the disease. The key benefit of this strategy is that no in-depth toxicological analysis is necessary because this knowledge, is at the very least, partially available in earlier literature. There are several licenced metal-based medications with positive traits and a tolerable toxicity profile that could be repurposed. Metallodrugs with a soft metal core that can firmly attach to target proteins' free thiol groups appear to be particularly appealing [28].

a. Auranofin-A gold based metal compound

To this purpose, we are assisting in the quick evaluation of Auranofin (AF) [2,3,4,6-tetra-o-acetyl-L-thio-D-glycol-pyranosos-S-(triethyl-phosphine)-gold(I)] (brand name: Ridaura®), AF (Figure 16) hereafter, a gold(I) medication with a history of clinical success. The FDA approved the medication AF in 1985 for the treatment of rheumatoid arthritis. It works primarily by modulating the immune system. The toxicity profile of AF is acceptable and it is safe to use on humans. There is still disagreement over the precise nature of AF's multi-targeted mechanism of action. However, there is growing consensus that Thioredoxin Reductase 1 should be the main target, causing disruption of the major oxidoreductase pathways, dysregulation of intracellular redox homeostasis and induction of Reactive Oxygen Species (ROS). The proteasome should be considered a secondary but nonetheless significant target [30, 31, 32]. AF, a simple gold (I) drug, is taken orally [28].

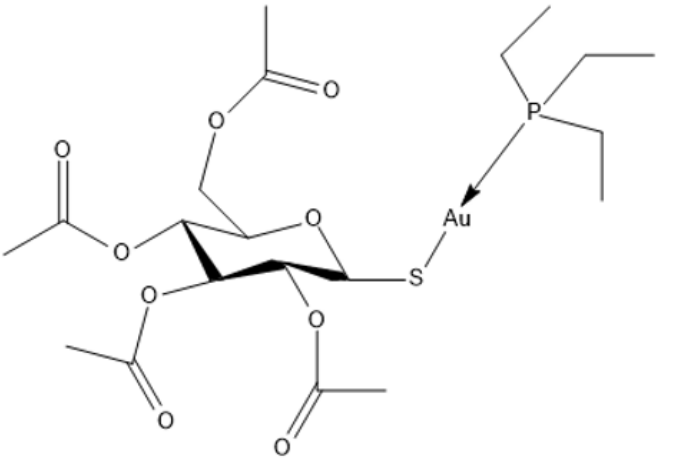

Fig. 16. Structure of Auranofin.

Due to its adaptability and potential to be used for a variety of therapeutic purposes, such as an antibacterial, anticancer or antiparasitic drug, AF has attracted significant research in recent years [30]. AF began clinical trials as an antiviral drug in response to reports of significant activity against HIV. Recalling that AF was found to have more efficiency than hydroxychloroquine and chloroquine in the treatment of HIV infection in inhibiting many viral production, latency and reactivation processes as well as decreasing the viral reservoir [32, 33]. Similar to Tocilizumab, it has been claimed that AF interferes with the interleukin 6 signaling by blocking the phosphorylation of JAK1 and STAT3, inhibits a few specific proteases and binds preferentially to free cysteine residues in proteins such as those found in cysteine proteases [32, 34].

With a stunning 95% reduction in viral RNA, AF substantially prevents SARS-CoV-2 multiplication in human cells. According to earlier findings, pairwise analysis revealed that in human cells AF significantly minimizes the production of SARS-CoV-2 induced cytokines. Due to its advantageous and multi-target mechanism, AF may be a helpful medicine to prevent the dispersal of SARS-CoV-2 and cure the associated pneumonia [32].

1.11

4.3. Mechanism of Action

Recent studies have shown that AF's mode of action consists of the induction of severe intracellular oxidative stress and redox dysregulation, both of which are mediated by the inhibition of Thioredoxin Reductase and the induction of mitochondrial dysfunction. Inhibition of the proteasome and endoplasmic reticulum stress were also outlined. For

pharmacological repurposing as an anticancer agent or for the treatment of Schistosomiasis and other infectious illnesses, AF has gained increasing interest in recent years. Additionally, it became active against HIV and was used in antiretroviral clinical trials. Importantly, AF is more efficient than hydroxychloroquine at treating HIV; also, its increased activity is linked to a better pharmacokinetic profile. This drug is being used to treat COVID-19 disease.

4.4. Methodology

This proposal is based on in vitro findings demonstrating that AF effectively inhibits the replication of SARS-CoV-2 while reducing inflammation in human cells. The methodology followed in these studies is outlined as follows:

Initially infected Huh7 cells, a hepatocyte-derived carcinoma cell line, with the SARS-CoV-2 virus. The infected cells were then treated with 4 µM of AF, and supernatants were collected at intervals of 24 and 48 hours. RT-PCR analysis was used to quantify the viral RNA copies. The results showed a significant reduction in viral RNA in the supernatants, with a 70% decrease at 24 hours and an 85% decrease at 48 hours. Intracellular viral RNA levels also showed marked reductions, dropping by 85% at 24 hours and 95% at 48 hours. Importantly, Huh7 cells displayed good tolerance to AF at the tested doses.

AF demonstrated an EC50 of approximately 1.5 µM in preventing SARS-CoV-2 replication within infected cells. Furthermore, AF significantly suppressed the production of SARS-CoV-2-induced cytokines in Huh7 cells. Specifically, AF-treated cells exhibited only a 2-fold increase in IL-6 expression, compared to a substantial increase in IL-6 mRNA expression in untreated, infected cells—a factor linked to severe lung inflammatory symptoms. These findings collectively suggest that AF is a promising candidate for the treatment of COVID-19.

4.5. Bismuth and antimony based metal compound

Additionally, a small number of therapeutically approved Bismuth (Bi) and Antimony (Sb) compounds with unusual reactivity traits, a strong thiophilic nature, and a tolerable safety limit should be considered in this type of evaluation. It is important to remember that Hongzhe Sun et al. conducted a thorough investigation into the effectiveness of Bi compounds against the SARS-CoV virus a few years ago. Some of those substances were particularly good at preventing the SARS-CoV virus's helicase and protease catalytic activity. They discovered that the number of Bi-based complexes having polydentate ligands that contain N and O, such as porphyrin complexes, are characterized by potent inhibitory actions against Helicase ATPase (IC50 of about 0.5 µM). It's interesting that when the inhibitory activity of complexes bearing various ligands was compared-which is naturally connected with a variable stability-it was discovered that the Bi center is crucial in producing the inhibitory effects. Porphyrin complexes were shown to be the most efficient at gradually suppressing the helicase unwinding activity to the duplex upon the addition of increasing quantities. The SARS helicase duplex unwinding produced by Bi complexes was also measured.

4.6. Ruthenium based metal compound

In addition to Bi, the experimental Ruthenium (Ru) anticancer agents New Anti-Tumor Metastasis Inhibitor (NAMI A) and (sodium trans-[tetrachloridobis (1H-indazole) ruthenate (III)]) KP1339 (Figure 17) may also be candidates for anti-COVID testing. NAMI A and KP 1339 have already been approved for use in clinical trials for the treatment of cancer, and they have proven to be pretty safe at high concentrations. Later, NAMI A was removed from clinical testing because the chosen cancer model had only moderate anticancer effectiveness. Studies are currently being conducted to determine how well these Ru compounds suppress in vitro SARS-CoV-2 replication [28].

4.7. COVID-19 virus inactivation using Copper and its alloys

Due to its outstanding antiviral and antibacterial capabilities, Copper (Cu) and its alloys are potential components in the fight against the COVID-19 virus and many other microbiological pandemics. Even though numerous studies have demonstrated that Cu and its alloys have antiviral characteristics, further study is still needed in this area. Numerous investigations on Cu and its alloys have shown that they offer significant promise for reducing the spread of infectious diseases. Furthermore, current research suggests that the covid-19 virus can be successfully inactivated by these alloys. Overall, the usage of Cu-based materials can be advantageous in the prevention and treatment of COVID-19 virus.

Surfaces made of Cu and its alloys are mostly vulnerable to the COVID-19 virus, which was the source of the most recent epidemic [35, 36]. Cu surfaces' antibacterial qualities can be considered as having a substantial impact on the prevention of infections. By preventing the spread of surface pollution, antimicrobial metallic Cu surfaces can thereby protect against infectious bacteria [36, 37]. The virus is easily inactivated on Cu, as well as a variety of Cu-Zn and Cu-Ni alloys. A number of biological activities call for Cu, as an essential mineral. The majority of Cu in healthy humans is directly bonded to the prosthetic groups of proteins or enzymes. Cu-containing substances have been employed as antimicrobials from the time of the ancient Roman and Egyptian cultures. Hospitals currently use Cu alloy surfaces to lessen the spread of hospital borne diseases, and Cu-based medicines are designed to cure human fungal infections and shield crops from bacterial and fungal pathogens. Animals have built-in defense mechanisms that use Cu against microorganisms [38, 39]. As a result, Cu is thought to be

essential for development and upkeep of the immune system [36, 40]. Several factors make Cu a potent weapon to combat COVID-19 and upcoming pandemics. These alloys can be utilized often in public location on common touch surfaces, especially in areas with high human activity. Although utilizing Cu for frequently handled surfaces does not eliminate the need for sanitization, using Cu for railings, doors and cabinet handles, is a passive method to reduce the amount of time that viruses can survive on the surface.

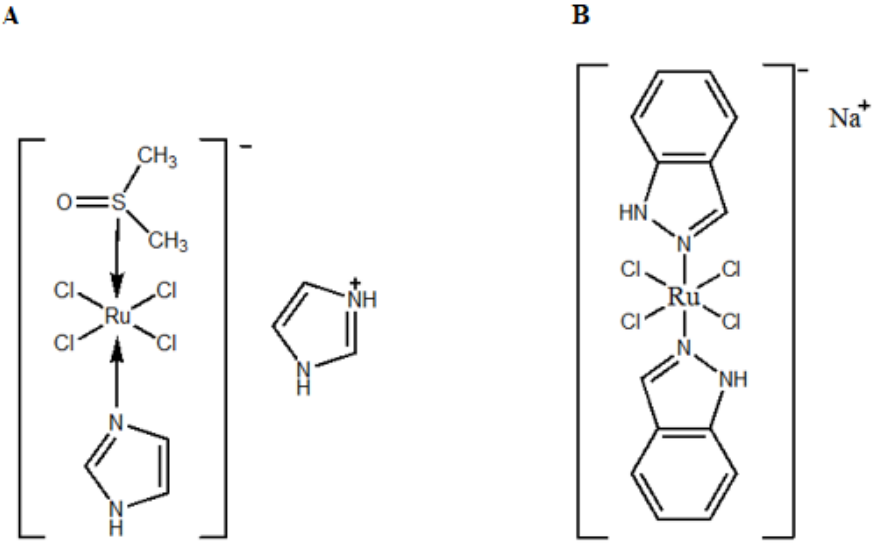

Fig. 17. Structure of **(A)** NAMI A and **(B)** KP1339.

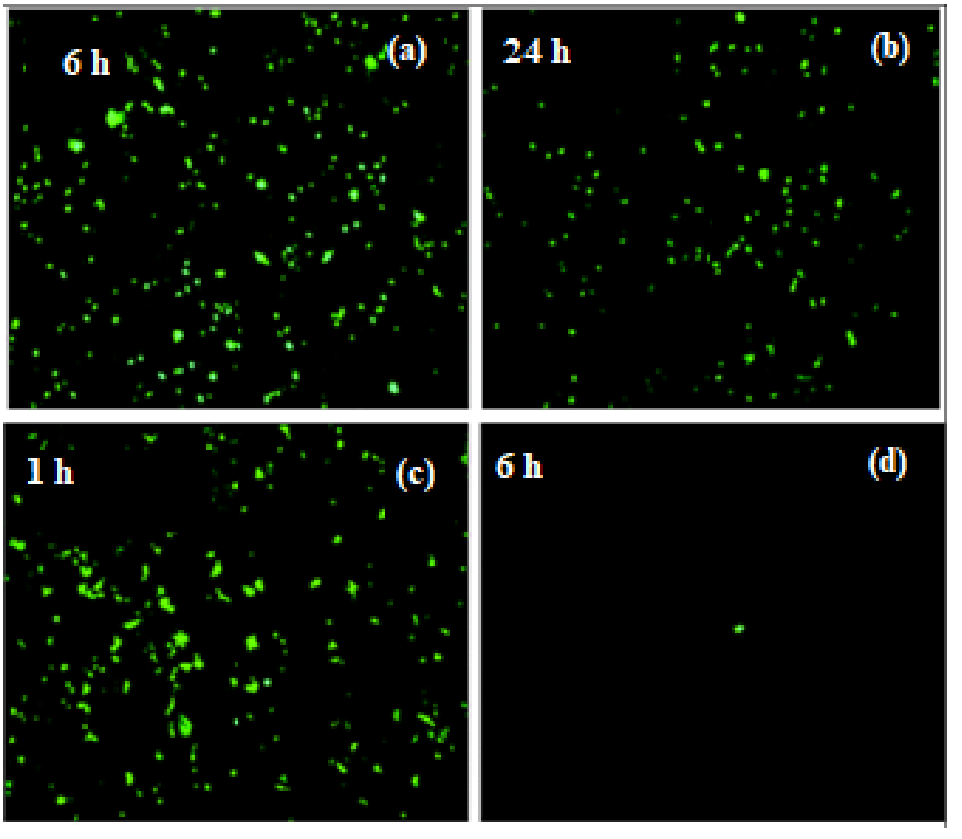

Fig. 18. Infectivity of the Influenza virus when exposed to **(a, b)** surfaces made of stainless steel and **(c, d)** surfaces made of Cu. Reprinted with permission from ref. [36] Govind, V., Bharadwaj, S., Sai Ganesh, M.R., Vishnu, J., Shankar, K.V., Shankar, B. and Rajesh, R. **2021**. 'Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review', *Biometals*, 34(6), pp.1217-1235. Copyright @ Springer Science.

4.7.1. Antiviral properties of Cu against COVID-19

Due to its toxicity, Cu is a potent antibacterial agent [36, 39]. The innate immune system produces toxins to stave off microbial invasion (such as reactive oxygen species (ROS) and nitrogen species) as well as withholds nutrition to starve the invading bacteria as part of its defence against pathogens. Cu has the potential to be hazardous due to its capacity to produce ROS [36, 41]. The Coccolithovirus lytic cycle is disrupted by Cu, and ROS production is increased as a result [36, 42]. Exposing pathogenic bacteria to Cu toxin, an efficient killing mechanism, within the host and is one of the innate immune system's protection strategies. On Cu surfaces, the amount of Influenza A virus particles was dramatically reduced.

Viral genomic DNA will be harmed as a result of Cu cross linking and ion binding between the genome's strands [36, 43]. Thus, the combined effects of Cu ion attack and ROS production lead to a successful deactivation. Products containing Cu have the power to greatly reduce the quantity of microorganisms in the medical environment [36, 44]. It is extremely essential to understand how Cu compounds affect DNA activity as DNA being the potential target for cytostatic medicines. The binding capacity of DNA and Cu (II) complexes' and their nuclease activity when present with reducing chemicals have long been known. It is believed that a Fenton type reaction in which ROS are produced is what causes DNA to degrade. The sort of organic ligands utilized in these Cu complexes affects and regulates their behavior [36, 45]. By deteriorating their genomic and plasmid DNA, Cu kills microbes. No viable microorganisms were found on Cu surfaces after a protracted period of incubation, indicating that contact killing happens at a rate of atleast7-8 logs h^{-1} [36, 37]. Cu is a powerful antibacterial substance [36, 37, 39, 45].

The intervention of Cu ions causes the viral nucleic acid to breakdown when a virus is exposed to a Cu surface [36, 45]. Sagripanti et al. discovered that the addition of peroxide increased the ability of Cu (II) ions to inactivate five enclosed or non-enveloped, single or double stranded DNA or RNA viruses. Cu peroxide was found to have a greater degree of virucidal activity after the introduction of peroxide in comparison to Fe (III) ions, indicating that it is a potent antibacterial agent against the UX174, U6, T7, Herpes and Junin Simplex virus. The antibacterial behavior of Cu surfaces was superior to that of stainless-steel surfaces. Noyce et al. examined the amounts of Influenza A virus contamination on Cu and stainless-steel surfaces following exposure time of 1, 6 and 24 hours. Even after a 24-hour incubation period, the stainless surface showed a greater contamination level of 500,000 viral particles, as seen in Figure 18a, b. While only 500 virus particles were present on Cu surface (Figure 18c, d) after only 6 hours of incubation, demonstrating that Cu has better antibacterial properties [36, 43].

In a related experiment, Michels et al. [36, 46] found that when compared to other materials, Cu alloy surfaces significantly reduced bacterial activity by 83%. Even after five minutes of exposure, there was a full loss of infectious activity on the Cu alloy under examination. In addition to being simple, inactivation was also accompanied by severe structural damage and irreversible RNA damage to the virus [36, 47]. By exposing the viral genomes to Cu, the virus's shape was permanently altered, leading to the rupture of the envelope and the distribution of surface spikes. When compared to non-enveloped viruses on Cu, the activation was brought on by Cu(I) and Cu (II) ions and facilitated by ROS production on Cu alloy surfaces. In Figure 19a, the contact killing mechanism is shown schematically [36, 48].

Figure 19b by Grass et al. depicts one of the methods by which the Cu ions aid in killing the bacteria. According to observations made by Grass et al. [36, 37] and Warnes et al. [36, 49], the virus is killed by the cell's metabolism, respiration and reproduction being restricted as well as by Cu ions "entering" the cell and destroying its DNA. The quick killing of bacteria, viruses and yeast on metallic Cu surfaces gave rise to the term "contact killing" [36, 37] whereby the bacteria that are present on the surface absorb significant amount of the Cu ions, resulting in cell damage. The cytoplasmic material inside the cell is then lost as a result of the cell membrane rupturing. These Cu ions also lead to the production of ROS, which further harms the cell. Another approach is the use of extremely thin sheets with "sharp edges" that can pierce cell membranes and destroy them. One such substance with this characteristic is graphene. According to a recent study by Selvamani et al. [36, 50], Cu surfaces can be laser-treated to create rough textures, which increases the Cu's surface area and in turn rises its antibacterial activity.

Numerous studies have examined the potency of Cu and its alloy surfaces for antiviral action in light of the requirement to eradicate the COVID-19 virus on the surface of the materials [35, 36, 46, 49]. After a specific amount of the virus' exposure to Cu ions in Cu coupons [35, 36]. Researchers [36, 49] detected the number of virus (measured by Plague Forming Units, PFU). Brass alloy with more than 70% Cu shows higher viral activity against HuCoV-229E when compared to other materials. Within a shorter period of 60 minutes, there was essentially no sign of the infection on the surface. On the other hand, it required atleast 5 days at the RT for the virus to be completely eradicated from other household items like Teflon, stainless steel, PVC (polyvinylchloride), ceramics and glass. Additionally, the alloy's effectiveness in virucidal behavior, as demonstrated in Figure 20, was related to the amount of virus that persisted on the surface. The lowered virucidal activity of Zn and Ni alloys was similar to that of stainless steel. A similar investigation evaluating the stability of SARS-CoV-1 and 2 in plastic, aerosol, stainless steel, Cu and cardboard was recently carried out by Doremalen et al. [35, 36] The outcomes demonstrated Cu's antiviral impact to be similarly effective. Even after 72 hours, the SARS-CoV-1 and SARS-CoV-2 traces, however, were not discovered on Cu surface after 8 and 4 hours, respectively. The quantity of viruses on the surface diminishes over time, as seen in Figure 20a, b. Table 1 compares Cu's antiviral properties to those of other materials [36, 49].

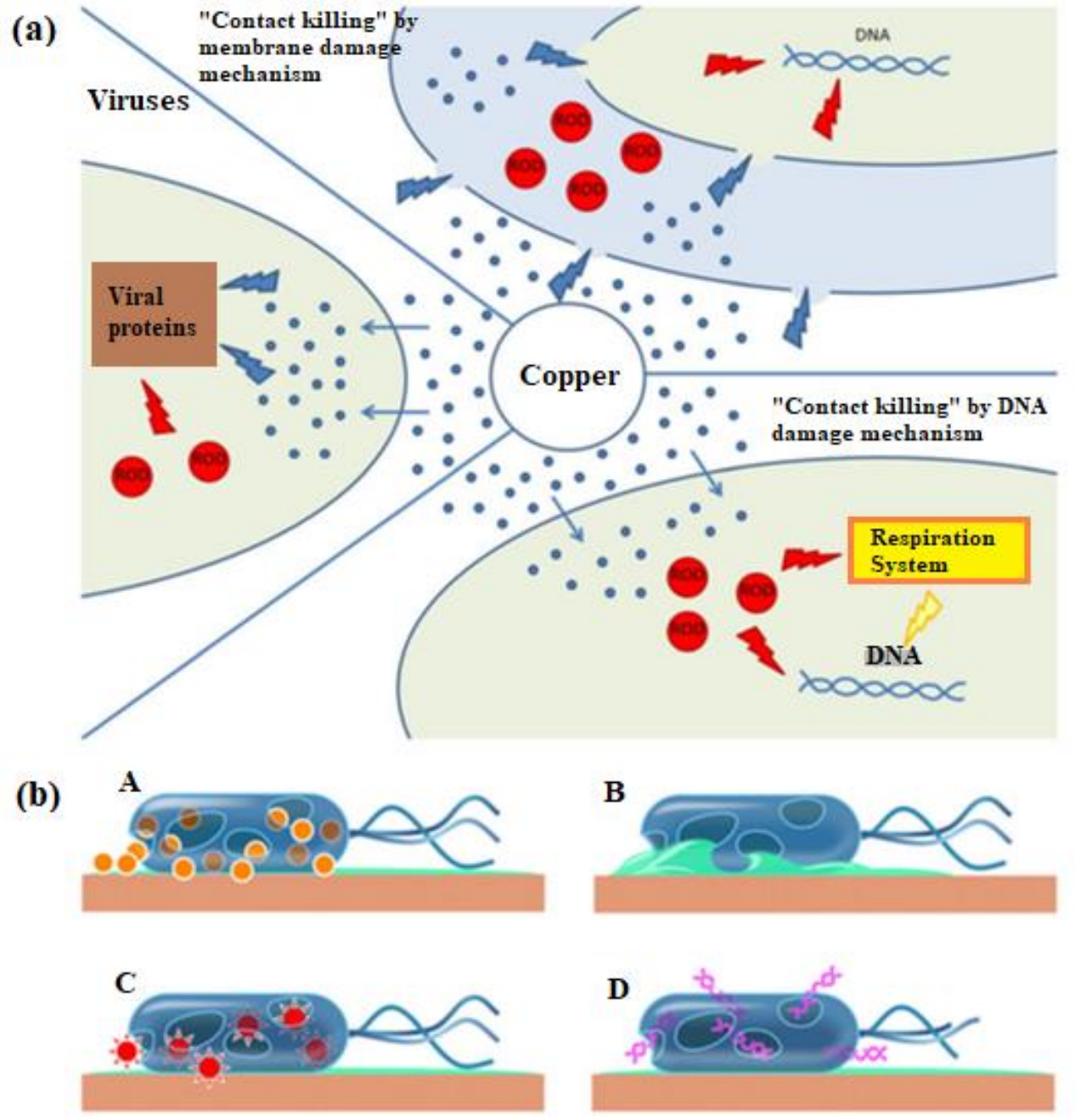

Fig. 19. **(a)** Contact killing mechanism of Cu against bacteria (top), virus (middle) and fungus (bottom), **(b)** Illustrations of contact killing mechanism on a Cu surface (a) rupture of cell. membrane, (b) loss of cytoplasmic content, (c) generation of other ROS by Cu ions. Reprinted with permission from ref. [36] Govind, V., Bharadwaj, S., Sai Ganesh, M.R., Vishnu, J., Shankar, K.V., Shankar, B. and Rajesh, R. **2021**. 'Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review', *Biometals*, 34(6), pp.1217-1235. Copyright @ Springer Science.

Table. 1. Antiviral properties of Cu against other materials [36].

S. No	Material	Effectiveness of material in comparison to Cu	Virus tested
1	FeH_2O_2	Viruses were resistant to FeH_2O_2 in comparison to metallic CuH_2O_2	ϕ4X174, T7, +6, Junin and herpes
2	Brass	Covid-19 on brass was inactivated in 40 min or less	COVID-19
3	Glass	COVID-19 will linger for 4 days	COVID-19
4	Ni	Relatively ineffective inactivation	COVID-19
5	Plastic	Up to 72h	COVID-19

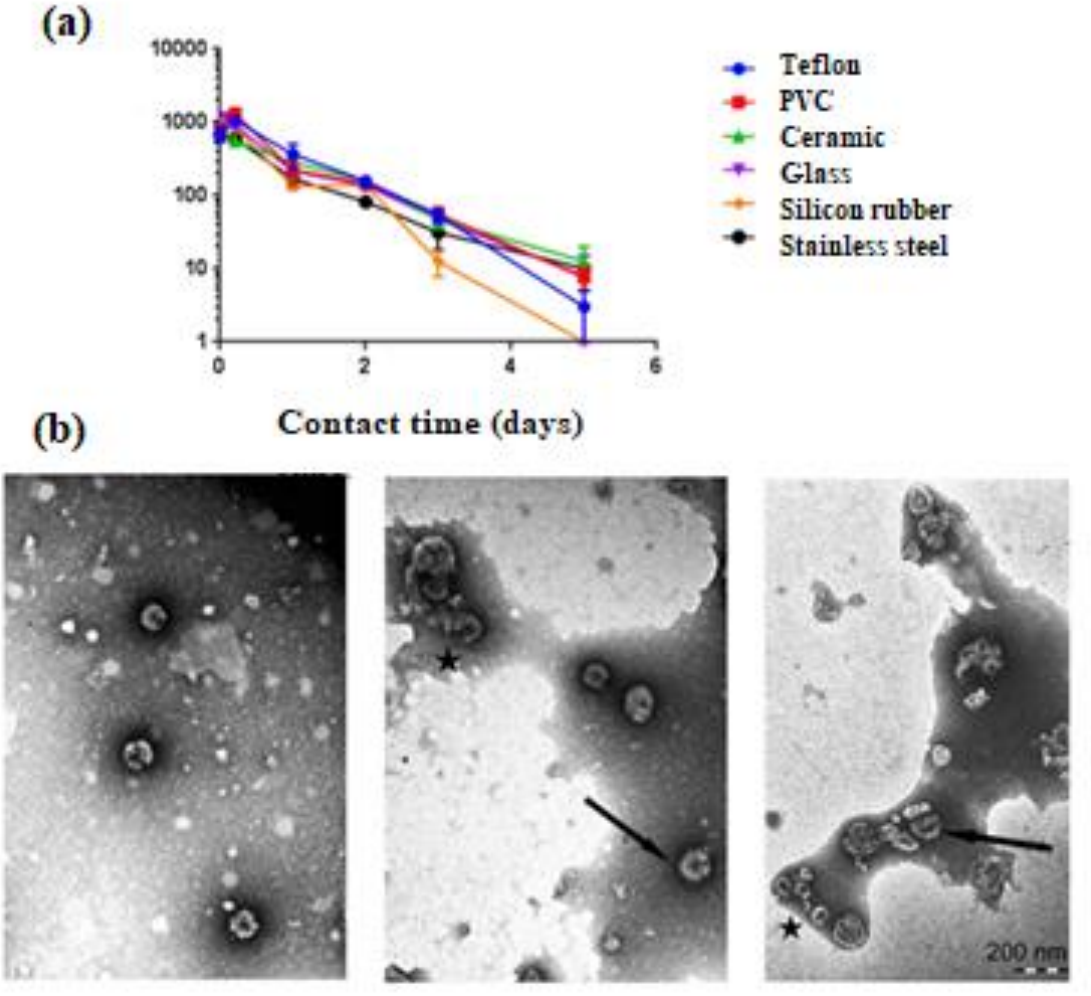

Fig. 20. (a) A comparison of the virucidal effects of various surfaces, **(b)** The COVID-19 virus contact with stainless steel for 10 minutes, the virus disintegrating on a Cu surface after 10 minutes, and the virus shrinking with surface spike damage after 30 minutes. Reprinted with permission from ref. [36] Govind, V., Bharadwaj, S., Sai Ganesh, M.R., Vishnu, J., Shankar, K.V., Shankar, B. and Rajesh, R. **2021**. 'Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review', *Biometals*, 34(6), pp.1217-1235. Copyright @ Springer Science.

4.8. SARS-CoV-19 inactivation by silver (Ag)

Metals like Ag, Cu and Zn have inherent antibacterial qualities and are already present in medical devices and healthcare facilities. For instance, Ag is utilized in intravascular and urinary catheters as well as wound dressing. Because Nanoparticles (NPs) release the toxic metal ions gradually and precisely where the antimicrobial action is needed and because NPs can accumulate inside cells without being eliminated by specialized efflux pumps, it is favorable to use NPs made of these metals rather than bulk materials or the metal ions themselves. Historically, Ag has been employed for its antibacterial properties in medical applications [14, 51] and more recently, as a biocide, in commercial items like Ag zeolites in paints [14, 52] and food trays [14, 53]. Ag NPs have shown to be effective against a number of viruses, including HIV-1[14, 54], the monkey pox virus [14, 55], the bacteriophages UZ1 and MS2, the Marine NoroVirus (MNV1) [14, 56, 57] the Human Simplex Virus (HSV), [14, 58] the Human Brucellosis Virus (HBV) and more recently the Porcine Epidemic Diarrhea Virus (PEDV) [14, 59].

4.8.1. Antiviral properties of Ag NPs

Ag NP's antiviral effects result from three distinct pathways. First, the dissolution of Ag (0) causes the release of some harmful Ag (I) forms, such as Ag^+ ions, which may be the cause of their antiviral action. Interaction of Ag with thiols form small molecules like cysteine or glutathione as well as with sulfhdryl groups in the active sites of many enzymes as it is a soft metal with a significant affinity for sulphur. The activity of thiol containing enzymes that are engaged in viral

replication may be hampered by interactions between Ag (I) and surface proteins of viruses or by Ag (I) accumulation in host cells. In response to MNV-1 exposed to Ag NPs, De Gusseme et al. and Zodrow et al. developed this theory to explain the antiviral activity of Ag NPs for bacteriophage MS2 [14, 56, 60]. Additionally, Ag_2S nanoclusters (NCs) with diameter of 2.5nm 4nm effectively inhibited PEDV replication in Vero cells by preventing the production of vial negative strand RNA and virus budding from the cells, but not by preventing the virus' anchoring to cell membranes or its penetration inside the cell. The authors came to the conclusion that the antiviral function of Ag NCs was independent of the release of Ag after finding that exposing cells to Ag^+ ions at the same concentration did not prevent replication of virus [14, 59]. However, because the mechanism through which Ag^+ ions and Ag NCs enter cells differ, so would their local distribution and management within cells. This distinction might cause Ag ions and Ag NCs to behave in various ways toxically toward cells that have been infected by viruses. Ag(I) could gather in different places of cells or be quickly removed, whereas, Ag NCs may aggregate in intracellular regions where crucial viral cycle phases are carried out, like protein and genome synthesis or assembly of nucleocapsids prior to their release into the extracellular environment. Secondly, Ag NPs antiviral effectiveness would result from direct physical contact with virus surfaces, which would prevent viruses from docking on host cells and reduce their infectious potential. For HIV-1 exposed to 1-10nm [14, 54] and HSV-2 exposed 10 1333 and 46nm Ag NPs with tannic acid, respectively [14, 58], Elechiguerra et al. [14, 54] and Orlowski et al. respectively demonstrated this method. Elechiguerra et al. discovered that Ag NPs with an ideal size of around 10nm physically interacted with viruses more effectively than those with bigger or smaller NP sizes. However, Orlowski et al. discovered that larger the NP, more potently it blocked virus attachement to the host cell. De Gusseme et al. also postulated the same mechanism to account for the decreased infectivity of the MNV-1 virus when exposed to 11.2nm biogenic Ag NPs, together with the release of Ag(I) [14, 56]. The local release of ROS from the Ag NPs surface during this docking, if Ag NPs on the surface of viruses could also cause local virus membrane and/ or envelope damage. Ag NPs are already utilized in catheters, wound dressings and several other medical equipments; their usage could be foreseen to give paints used in healthcare settings, as well as face masks or air filters, biocidal qualities. Ag NPs placed on filters exhibit potent antiviral properties against the bacteriophage MS2, which decreases with dust loading [14, 61].

5. DRUG REPURPOSING STRATEGY USING VIRTUAL SCREENING

Regarding the first strategy, AF, a gold molecule used clinically to treat rheumatoid arthritis, has shown some extremely positive outcomes, at least in vitro. Similar to this, several Bi compounds seem to be quite promising. The second technique in undoubtedly more difficult and time-consuming, but it might present more options; it might be aided by considerations for pathway driven or target driven discovery [28]. Drug Repurposing technique was used to utilize virtual screening to find potential treatments for COVID-19 in light of the fact that it is a good strategy for pandemic viral infection. Five COVID-19 proteins were chosen as potential targets for therapeutic repositioning, including:

- 3-Chymotrypsin-Like protease (3CLpro)
- Papain-Like protease (PLpro)
- Cleavage Site
- Heptad Repeat 1 (HR1)
- Receptor Binding Domain (RBD) in (S) protein, were selected as target proteins for drug repositioning.

4.8.2. Methodology

First five COVID-19 proteins were constructed using homology modeling. Then, using virtual screening, 2471 FDA-approved medicines were checked for compatibility with the S protein's cleavage site and RBD. The cleavage site and RBD of S protein were linked to 128 FDA-approved medications that had the best free-binding energies. 18 of these 128 medicines have either been utilized as antivirals recently or have been suggested to have antiviral properties. The 18 chosen medications were then subjected to virtual screening using ACE2, 3CLpro, PLpro, HR1 and TMPRSS2 (Figure 21) [62].

Phylogenetic analysis of the entire viral genome was carried out to better understand this new virus (29,903 nucleotides). The findings showed that the new virus shares 89.1% of its nucleotides with the subgenus Sarbecovirus of the genus Betacoronavirus, which previously caused the severe epidemic known as SARS. The S protein of this new virus, COVID-19 is one of those that can encourage the fusion of viral and cellular membranes. As a result, it makes it easier for the corona virus to enter the host cells.

(S) Protein with 1288 amino acids consist of S1and S2 subunits, it facilitates the union of the viral and host cell membranes. These components include the Transmembrane Domain (TM), HR 1, Heptad Repeat 2 (HR 2), RBD Fusion Peptide (FP) (CP). S1 is essential for attaching to cellular receptors, whereas S2 can promote viral fusion and entry. S1 and S2 have different roles in this entry. ACE2 is linked via a conserved RBD, which is known to interact with 14 amino acids in the S1 of SARS-CoV.

Additionally, research indicates that ACE2 is a COVID-19 receptor. Furthermore, cellular tropism and pathogenicity depend on the sequence variations of the (S) protein cleavage site. The pathogenicity of viruses is influenced by the cleavage site in the (S) protein sequence. The COVID-19 S-protein sequence comprises 12 additional sequence upstream to the single Arg^- cleavage site 1, resulting in the solvent-

exposed PRRARSV sequence, which resembles a cleavage site. This novel cleavage site is the cause of the virus's efficient proliferation among the populace. This mechanism was absent in earlier corona virus.

As we already established, COVID -19's S2 subunit is in charge of facilitating viral fusion and entry into host cell. HR 1 and HR 2 interact in a way that affects cellular membrane and causes fusion. The COVID-19 S2 HR1 and HR2 interaction pattern variation (in terms of fusion with cell membrane) are brought on by mutations in the HR 1 core area; 8 out of 21 residues show mutation (38% difference).

For COVID-19, ACE2 may also serve as the host receptor, according to the current speculation. Perhaps the degree and pattern of ACE2 expression in tissue contributes to the susceptibility, symptoms and outcome of COVID-19 infection. Recent studies indicate that Asian males express more ACE2 when single-cell RNA-sequencing (RNA-seq) is used to analyze the data. While entering the host cell, COVID-19 uses ACE2 as a receptor and the TMPRSS2 for priming the (S) protein. The viral (S) protein is activated by TMPRSS2, which promotes the fusion of the virus and the cell membranes. Human ACE2 residues surrounding lysine 31, tyrosine 41, 82-84 and 353-357 are crucial for corona virus S-protein binding. Because ACE2 expression was higher in Adipose Tissue than in lung tissue, the adipose tissue may not be as strong in terms of COVID-19.

The researchers found that, when looking at five different cancer types, the expression of ACE2 in noticeably higher in tumor tissues than in surrounding tissues. Therefore, it is recommended that patients with these five forms of cancer and those who are obese be given priority during COVID-19. It should be noted that ACE2 expression is favorably correlated with age and is related to both gender and age.

The transcription of COVID-19 genome results in the production of an eight hundred kDa polypeptide. Different proteins are created by cleaving this polypeptide. Proteolytic processing is aided by the enzyme PLpro and 3CLpro. The cleavage at the N-terminus the replica polyproteinsare caused by PLpro. In the corona virus family of viruses, 3CLpro plays a significant role and is well-preserved. Nonstructural proteins required for viral replication are generated by 3CLpro, which activates the polyproteins at 11 different locations. Researchers closely monitor 3CLpro in order to identify anti-viral properties in chemicals since this process would lay the groundwork for virus replication [62].

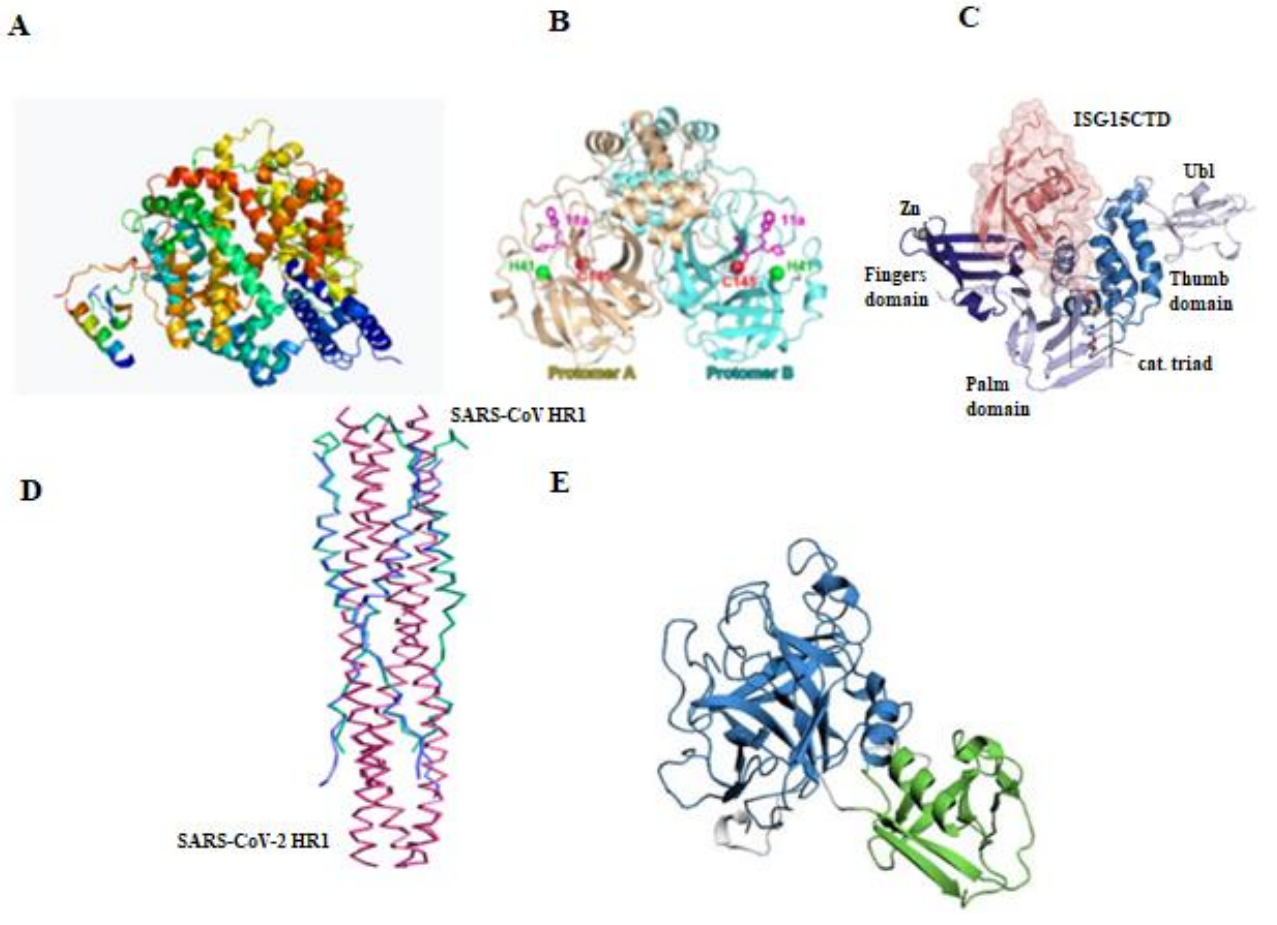

Fig. 21. Structures of (A) ACE2, (B) 3CLpro, (C) PLpro, [63] (D) HR1 and (E) TMPRSS2. Reprinted with permission from ref. [64] Fraser, B.J., Beldar, S., Seitova, A., Hutchinson, A., Mannar, D., Li, Y., Kwon, D., Tan, R., Wilson, R.P., Leopold, K. and Subramaniam, S. **2022**. 'Structure and activity of human TMPRSS2 protease implicated in SARS-CoV-2 activation', *Nature chemical biology*, 18(9), pp.963-971. Copyright @ Nature.

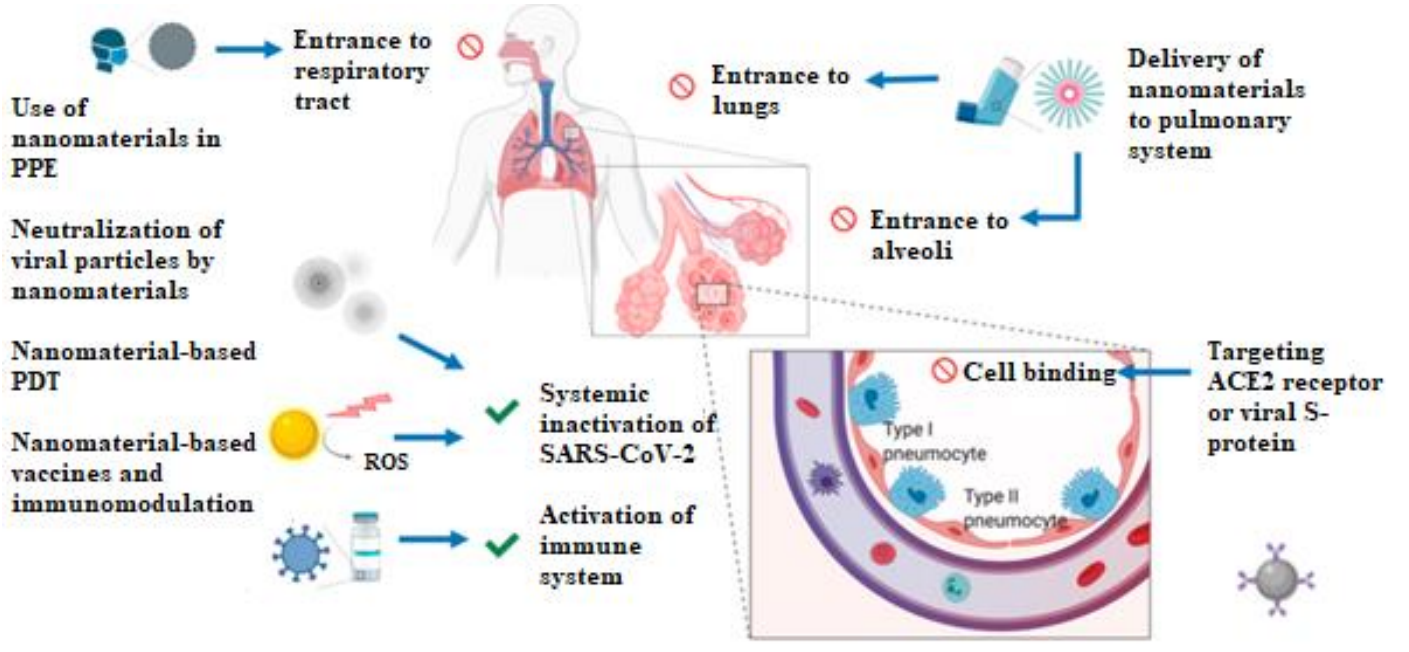

Fig. 22. Prevention and treatment of COVID-19 with nanomaterials. Reprinted with the permission from ref. [14] Weiss, C., Carriere, M., Fusco, L., Capua, I., Regla-Nava, J.A., Pasquali, M., Scott, J.A., Vitale, F., Unal, M.A., Mattevi, C. and Bedognetti, D. **2020**. 'Toward nanotechnology-enabled approaches against the COVID-19 pandemic', *ACS Nano*, 14(6), pp.6383-6406. Copyright @ American Chemical Society.

6. CONTROLLING SARS-COV-2 WITH NANOTECHNOLOGY

A number of platforms based on nanotechnology have already shown promise in preclinical studies to successfully combat a number of human viral pathogens, including HIV, the human papilloma virus, herpes simplex and respiratory virus. Nanotechnology offers multiple solutions to combat both internal and external viruses [14, 63-66]. In a number of ways, nanotechnology-based strategies should be used to fight COVID-19 and any upcoming pandemics as shown below in Figure 22, including:

(i) Novel vaccines and medications, where nanomaterials can be used to enhance targeted lung therapies and to directly deliver broad-spectrum antivirals;
(ii) Very accurate, quick and sensitive immunological testing (serological testing);
(iii) Ultra-fine filters for blood filteration or face masks;
(iv) New surfaces or surface coatings that can inactivate viruses and are resistant to viral adherence and the development of contact tracing tools.

Nanomaterials can be incorporated into Personal Protective Equipment (PPE) to stop SARS-CoV-2 from entering the respiratory system. Drug delivery to the pulmonary system via inhalators may also be accomplished with the aid of nanomaterials. By targeting ACE2 receptors or the viral (S) protein (as shown above in Figure 22), targeted NPs can prevent viral particles from binding to the cells in the alveoli. Viral particles can be systematically inactivated using a variety of techniques, such as neutralizing NPs or photocatalytic NM. Immunomodulation or vaccinations based on nanomaterials may be utilized to inhibit SARS-CoV-2 infection or even to enhance the immune response once an infection is present.

This crises has also brought attention to the value of quick prototyping and manufacturing for meeting unforeseen needs, such as in the event of a pandemic, where large scale manufacturing of equipment like PPE and ventilators are urgently required and nanotechnology may help (e.g. in the provision of easily synthesizable materials for the production of equipment as well as the enhancement of its effectiveness and durability).

6.1. SARS-CoV-2 inactivation in patients using nanotechnology tools

Numerous nanomaterials have been created for use in nanomedicine, including polymers [14, 67] dendrimers [14, 68] oligomers, NPs [14, 69] liposomes [14, 70] and small molecules [14, 71]. The fact that these medicines lose effectiveness with dilution when the virus chemical complex dissociates, allowing viruses to begin their replication cycle, has prevented their clinical translation. Recently, it has been demonstrated that this restriction can be removed by creating NPs that, once bound, are capable of permanently harming the virion to reduce viral infectivity irreversibly, reigniting

the search for a true, broad spectrum antiviral medication [14, 72].

6.2. Immunomodulation and Vaccine Development Using Nanomaterials

Several businesses are developing nanoliposome-encapsulated mRNA vaccines for SARS-CoV-2 that encode proteins like the (S) protein and have unique physicochemical characteristics that may be similar to those used for tumor antigen vaccination. Designing such nanocarriers is a difficult task that will take some time before they are clinically used since they must avoid being recognized by scavenger cells and be nontoxic and nonimmunogenic [14, 73].

a. Moderna

In a record-breaking 63 days after sequence selection, Moderna, in collaboration with National Institute of Health US enrolled first participants in a Phase I clinical trials evaluating mRNA vaccine (Mrna-1273) enclosed in lipid nanoparticles on March 16th, 2020 (NCT04283461). On April 16, 2020, the first batch of participants-healthy subjects aged 18 to 55 had completed their enrolment [14, 74].

b. CureVac and BioNTech

Similar vaccines were being developed by Cure Vac and BioNTech (in collaboration with Pfizer); Pfizer and BioNTech, in particular, have begun recruiting for phase I/II studies (NCT4368728, NCT04380701). A DNA plasmid vaccine developed by Inovio Pharmaceuticals (INO-4800) has entered Phase I testing in humans after demonstrating encouraging outcomes in mice and guinea pigs (NCT04336410) [14, 75].

c. AstraZeneca

University of Oxford and AstraZeneca developed a different candidate for COVID-19 vaccine for a Phase I clinical study (NCT04324606). The experiment included approximately 1110 participants and recruiting for it began at the end of April 2020. The vaccine was based on the SARS-CoV-2 (S) protein and the Chimpanzee Adenovirus vaccination vector (ChAdOx1). Adenoviral vectors from chimpanzees have already been tested on tens of thousands of people with proven safety against various infections. 6 rhesus macaques exposed to high doses of SARS-CoV-2 have received ChAdOx1 so far, the vaccination could not prevent infections, but it did lessen the severity of illness: no evidence of virus replication was seen in the lungs and control animals has considerably lower rates of respiratory illness and no damage to lungs [14, 76].

d. Sinopharm

Phase I/II testing of an inactivated vaccine created by the China National Pharmaceutical Group (Sinopharm) in partnership with the Wuhan Institute of Biological Products was conducted (ChiCTR2000031809) and clinical testing of a second inactivated vaccine created in partnership with the Beijing Institute of Biological Products had been authorized (ChiCTR2000032459) [14, 77].

6.3. Promising Nanomaterials in the Fight against COVID-19

Proper PPE is essential for both personal healthcare and the general public to stop the transmission of SARS-CoV-2. Furthermore, a significant step in stopping the transmission of COVID-19 and other contagious diseases would be the manufacturing of face masks and other protective equipments that can not only trap the aerosol droplets but also immobilize and kill the virus. When placed on filter surfaces, new nanomaterials like Ag NPs exhibit potent antiviral activity against the bacteriophage MS2 and can assist in achieving this goal [14, 60].

7. CONCLUSION

COVID-19, caused by the novel coronavirus SARS-CoV-2, has presented an unprecedented global challenge, profoundly affecting health systems, economies, and societies. This review underscores the complexity of COVID-19 as a multi-systemic disease, with a spectrum of clinical manifestations ranging from mild symptoms to severe complications. Despite extensive global research, many aspects of the virus's pathophysiology and its long-term implications remain unclear, underscoring the need for continuous exploration. The therapeutic strategies currently under investigation include "Drug Repurposing," which offers immediate solutions by adapting existing medications, and the "Discovery Approach," which focuses on designing new, targeted treatments specifically for SARS-CoV-2. Each approach has unique advantages and challenges. While drug repurposing allows for rapid deployment, it is often limited by suboptimal efficacy or off-target effects. On the other hand, the discovery of novel drugs tailored to the virus can provide more precise and effective solutions, though it requires substantial time and resources. Metal-based compounds and metallodrugs have emerged as promising candidates due to their unique bioactivities, including antiviral, enzyme-inhibitory, and immune-modulatory effects. These compounds may play dual roles in directly combating the virus and enhancing the efficacy of existing treatments. However, challenges such as potential toxicity and the need for rigorous safety profiling must be addressed. The development of vaccines remains the cornerstone of pandemic control, but therapeutic interventions are equally crucial for managing active infections and preventing severe

outcomes. As the pandemic continues to evolve, there remain numerous unanswered questions, including the long-term effects of the virus, its potential mutations, and the best strategies for sustained disease management.

8. FUTURE PERSPECTIVE

Looking ahead, the focus should shift toward designing targeted, COVID-19-specific therapeutics using the "Discovery Approach." This strategy, motivated by detailed pathway analysis, holds the potential to develop precise and effective treatments. Metal-based therapeutics should remain a priority, with research directed toward improving their selectivity, reducing toxicity, and enhancing their antiviral efficacy. Studies should also explore the synergistic potential of combining metal compounds with existing antiviral drugs to boost therapeutic outcomes. Beyond drug development, global preparedness must be strengthened through collaborative research, manufacturing capabilities, and equitable distribution systems. Research should also aim to establish optimal dosages, evaluate the long-term safety of treatments, and address virus variants. Integrating basic science, clinical research, and public health strategies will be essential for addressing this pandemic and preparing for future global health emergencies.

CONFLICT OF INTEREST

Authors declared that they have no potential conflicts.

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ABOUT THE AUTHORS

Nabtahil Iqbal holds a Master's degree in Organic Chemistry, earned in 2024. Currently, she is a Quality Control Analyst and a member of the R&D team at Wenovo Pharmaceuticals, Pakistan, where she contributes to drug development and quality assurance processes. With three publications to her credit, her primary research focus lies in Medicinal Chemistry. Nabtahil is committed to furthering her research and expertise in the field, aspiring to make meaningful contributions to therapeutic advancements.

Dr. Fawad Ahmad is a distinguished professor at the University of Wah, Pakistan, with a Ph.D. from the University of Science and Technology of China, Hefei. With seven years of research experience, Dr. Ahmad specializes in catalyst preparation, fuel cells, and water purification. He is particularly renowned for his groundbreaking work on lithium-ion batteries and catalysts for fuel cells, making significant contributions to the field of physical chemistry.

Ms. Irum Jamil completed her MS in Organic Chemistry at the University of Wah, Wah Cantt, Pakistan, and is currently pursuing a Ph.D. in Chemistry from the same institution. Her research interests include the synthesis of materials and their applications in the medicinal field. With a dedication to advancing her expertise, Irum focuses on the development of innovative solutions in organic and medicinal chemistry.

Dr. Muhammad Imran Khan serves as a Research Scientist at the Research Institute of Sciences and Engineering (RISE), University of Sharjah, UAE. He earned his Ph.D. from the University of Science and Technology of China, Hefei, focusing on fabricating polymeric ion exchange membranes for water purification and fuel cells. Dr. Khan has published over 150 articles and is listed among The World's Top 2% Scientists (2021-2024). His work is widely recognized in the fields of environmental engineering and sustainable energy.

Dr. Abdallah Shanableh is a Professor of Environmental Engineering and the Director of RISE at the University of Sharjah, UAE. His expertise spans water and wastewater treatment, environmental monitoring, and waste management. With a career devoted to sustainability and innovation, Dr. Shanableh has made profound contributions to advancing environmental engineering solutions worldwide.

Dr. Aqsa Naz is a Ph.D. researcher at The Islamia University of Bahawalpur (IUB), Pakistan. She earned her M.Phil. in Chemistry from Government Sadiq College Women University, Bahawalpur. Her research is centered on wastewater purification, employing techniques such as adsorption and photodegradation. Dr. Naz is committed to environmental conservation and the development of sustainable water treatment methods.

Dr. Nosheen Farooq is a dedicated lecturer and researcher at Government Sadiq Women University, Bahawalpur, Pakistan. Her research spans electrochemical sensors, supercapacitors, and nanomaterials for energy storage. With over 30 peer-reviewed publications and active participation in scientific conferences, Dr. Farooq is known for her leadership and collaborative spirit. She holds a Ph.D. in Chemistry from The Islamia University of Bahawalpur and is a rising expert in materials chemistry.

Dr. Muhammad Babar Taj is an Assistant Professor of Inorganic Chemistry at The Islamia University of Bahawalpur, Pakistan. He earned his Ph.D. in 2017 from Quaid-e-Azam University, Islamabad. His research emphasizes Green Chemistry, focusing on mechanochemistry, hydrogen production, CO_2 reduction, and photocatalysis for wastewater treatment. With over 80 publications in esteemed journals, Dr. Taj is an influential figure in sustainable chemistry.

Prof. Dr. Mushtaq Hussain Lashari is a prominent zoologist serving as a Professor in the Department of Zoology at The Islamia University of Bahawalpur, Pakistan. Born in the Sardar Baloch Lashari tribe of D.G. Khan, he earned his Master's and Ph.D. degrees from Bahauddin Zakariya University, Multan. His research focuses on animal reproduction, parasitology, and nephrology. Prof. Lashari has published 150 articles and supervised over 180 M.Phil. and 11 Ph.D. students, leaving a significant impact on zoological sciences.

Dr. Suryyia Manzoor is an Associate Professor at the Institute of Chemical Sciences, Bahauddin Zakariya University, Multan, Pakistan. She obtained her Ph.D. in Separation Science and Catalysis from UNICAMP, Brazil, through a TWAS-CNPq scholarship. With over 75 publications and a role as guest editor for esteemed journals, she has mentored numerous MS and Ph.D. scholars. Dr. Manzoor is recognized for her significant contributions to catalysis and sustainable chemistry.

