RECENT ADVANCES IN NOVEL ANTI-VIRAL DEVELOPMENT: A FOCUS ON COVID-19 THERAPEUTICS

Hari Priya Behera[1*], Alisha Patel[2], Harsh Vardhan Yadav[3], Chandrakanta Pandey[4], Sandeep Netam[5]

Assistant Professor, Department of Pharmacology, Danteswari college of pharmacy Borpadar, Jagdalpur-494221, Chhattisgarh, India.

B. Pharm Student, Department of Pharmacy Danteswari college of pharmacy Jagdalpur-494221, Chhattisgarh, India

Corresponding Author*: Hari Priya Behera

Abstract:

The rapid global spread of COVID-19 has underscored the urgent need for novel antiviral agents to combat emerging infectious diseases. This review highlights emerging trends in the development of antiviral therapies, with a particular focus on the advancements made in response to the SARS-CoV-2 pandemic. The development of antiviral agents has increasingly leveraged cutting-edge technologies, including structure-based drug design, artificial intelligence (AI), and genomic sequencing. Additionally, repurposing existing drugs and exploring natural compounds have become integral strategies. Key approaches include targeting viral enzymes, such as proteases and polymerases, modulating the host immune response, and inhibiting viral entry. The promising role of monoclonal antibodies, RNA-based therapies (such as RNA interference and mRNA vaccines), and combination therapies are also discussed. Despite significant progress, challenges remain in ensuring the global accessibility of antiviral treatments, overcoming viral resistance, and managing the complexities of viral mutations. This review outlines the progress made in the fight against COVID-19 and reflects on the broader implications for the future development of antiviral agents against viral threats**.**

Keywords: COVID 19, Antiviral agent, global health, Chronic, Medication, Pandemic, Infection, Development, RNA, DNA, Nucleotides, Prevention, Safety, Treatment, Viral infection, Plasma, Accumulation, Discoverey, Targeting.

INTRODUCTION: -

A pandemic such as COVID-19 highlights the necessity for novel antiviral medications that can lessen the effects of newly discovered illnesses (1). The dynamic nature of SARS-CoV-2, marked by high mutation rates and the disclosure of multiple of concern, has highlighted the limitations of existing antiviral strategies, despite rapid development of vaccines and therapeutics. therefore, an emergency need for new therapeutic agents with broad-spectrum activity, enhanced efficacy, and resistance mitigation. Through the focus on COVID-19, advancements in antiviral research have been catalyzed, including structure-based drug design,

and artificial intelligence (2). Further diversifying the therapeutic landscape are complementary strategies that modulate the immune response or target critical host factors for viral replication. An overview of emerging trends shaping the evolution of new antiviral agents opposed to COVID-19 is provided in this review, emphasizing their mechanisms of action, preclinical and clinical advances, and challenges that need to be overcome in order to combat not only SARS-CoV-2. (3,4).

It is anticipated that the first cases of coronavirus disease 2019 would be reported by the conclusion of December 2019. The virus is expected to spread quickly worldwide, resembling the terrifying "Spanish flu" pandemic that occurred 101 years ago (5). More than 6.45 million deaths. Some nations, nevertheless, handle this tumultuous condition more skilfully than others. The COVID-19 summary data verified the overall number of cases, fatalities, and mortality rate in the chosen industrialized nations. Vaccines are the most effective protection against pathogen outbreaks since The incidence of illness and mortality from a number of lethal viruses and bacteria have significantly decreased in recent decades (6). Several strategies have been used over time to create and produce vaccines against various viral diseases. The vaccines that are currently on the market can be manufactured from nucleic acids, live attenuated viruses, inactivated viruses, or purified antigens. Despite the variety of vaccine design alternatives, it often takes several years for a vaccine to move from the early design phase to approval and clinical use. Furthermore, only a very small fraction of candidates successfully advanced from preclinical research to clinical trials prior to the COVID-19 pandemic. Inadequate subject enrollments for testing are a significant barrier to vaccine development. As a result, businesses that create vaccines typically test their efficacy and safety on animals rather than people(7). Clinical trial success is significantly reduced when there is a dearth of suitable human safety data, and vaccines that do make it to clinical trials usually have a poor efficacy-to-safety balance.

Historical Background of Antiviral Agents:

The fight against viruses in global health has come at a heavy and agonizing cost. which is a vital tool in the fight against viral illnesses (8). There is strong evidence that HIV-1 antivirals have effectively turned a fatal illness into a chronic condition that can be managed. (9,10). Additionally, it has been demonstrated that influenza antivirals decrease the duration and lower mortality rates(11). people tend to overlook the miseries that come with a pandemic. Only a small number of known human viruses have received FDA-approved medications to combat their outbreak up to this point. However, under the strain of drug selection, viruses change quickly, greatly diminishing the therapeutic efficacy of already available medications. Thus, managing new viruses and overcoming treatment resistance are major obstacles in the creation of drugs that fight viruses.

In order to address current medicine aversion and the possible arrival of novel viral diseases in the future, this Special Issue on "Antiviral Drug Discovery" seeks to create an engaging environment for the crucial and pressing research concerns (12). This includes some of the most significant viruses, such as avian infectious bronchitis virus (IBV), influenza A virus, human immunodeficiency virus. Furthermore, this issue also discusses the potential of broad-spectrum antiviral drugs that target host factors (13,14).

SARS-CoV-2 antiviral medication discovery using in silico studies. In silico computer screening can assist us in more efficiently identifying the hit compounds than the time-consuming and expensive traditional drug development methods. emphasized the need for some experimental confirmation to sure the effectiveness and anti-resistance properties of the selected treatment options. discovered seven possible SARS-CoV-2 inhibitors with unique scaffolds using deep learning generative models. The method created by Andrianov serves as a guide for finding new compounds for potential pandemic and epidemic preparedness(15,16).

HIV-1 antiviral medication development that targets capsid protein and HIV-1 RT. Even though the death rate from AIDS has been successfully decreased by highly active antiretroviral therapy (HAART), growing drug resistance issues compel us to develop a new anti-HIV-1 medication (17,18). With an EC50 range from 11 to 246 nM, outperforming the commercially available NVP and EFV by a significant margin. Akther et al. used the newly FDA-approved CA inhibitor GS-6207 as the lead in their structure-based design that targets the HIV-1 capsid protein. Importantly, they devise a generic synthetic pathway that permits the modular synthesis of new GS-6207 subtypes, potentially aiding in the development and synthesis of additional molecules with enhanced potency(19).

Hemagglutinin 1-Mediated Virus Attachment is the goal of IAV antiviral medication discovery. Numerous influenza pandemics have left horrifying legacies in human history during the 20th century. As a result, IAV antiviral medications are important pandemic preparedness stocks. After screening 23 ginsenosides, discovered ginsenosides G-rk1 and G-rg5, which demonstrated antiviral properties against three IAV subtypes in vitro. they described the dose-dependent interactions between G-rk1 and HA1, offering a new technique for identifying IAV inhibitors (20).

Baicalin's mechanism of IBV inhibition. IBV primarily targets birds, notably broilers, endangering their ability to reproduce and causing significant financial losses for the poultry sector worldwide. In order to combat IBV, Feng et al. This would aid in the creation of antiviral medications.
Analysing how antivirals and the immune system interact when developing new antiviral medications (21). We have been reminded time and again of the significance of creating broad-spectrum antiviral medications by the advent or reemergence of viruses like Ebola, that have the potential to cause epidemics or pandemics. By preventing viral protein synthesis, that target host components effectively prevent the reproduction of the Corona, Flavi, Picorna, Filo, and Toga viruses. Unfortunately, there may be pleiotropic adverse effects associated with focusing on host characteristics. Ioxaglates may inhibit the eukaryotic translation initiation factor 4A (elF4A), as Schiffmann et al. showed [18]. This fascinating finding warns preclinical antiviral drug characterization that further research is need to fully understand how they interact with the immune system (22,23). The creation of antivirals that target HIV-1, IAV, IBV, SARS-CoV-2, and the investigation of how antivirals interact with the immune system, are the main areas of focus for this Special Issue's comparison of research and review articles on antiviral drug discovery. Finally, we would like to thank the staff and journal editors for their continued support (24).

The development of molnupiravir as a possible COVID-19 treatment: creating a direct-acting, oral antiviral medication during a pandemic

The necessary product profile was influenced by the pathophysiology of encephalitic alphavirus illness as well as the conditions around the potential application of an antiviral medication in public health or military contexts (25). Furthermore, the therapy candidate must, at minimum, be effective against the three alphaviruses that cause encephalitis. However, a broader variety of actions would be preferable to address additional RNA virus concerns (26). According to research on animals, VEEV can enter the central nervous system as soon as eighteen hours after being exposed to aerosols, therefore the onset of antiviral action would need to be quick (27,28). Furthermore, it is better if the medication is oral and self-administrable due to the potential negative effects that a soldier exposed to VEEV in aerosol form may have, or in the case of a large-scale VEEV zoonotic epidemic (29). Medication resistance should be hard to acquire in order to stop viral outbreaks and quick loss of function (30). From the perspective of counterterrorism, it is preferable for genetic alterations that are intentionally created or introduced through passaging studies to make it more difficult to build resistance to the antiviral medication. Lastly, considering the severity of infection-related morbidity and mortality, the drug's risk/benefit ratio should be acceptable. (31,32).

Although this product profile was created with encephalitic alphavirus disease in mind, it is evidently relevant to a different type of other RNA viruses. (33). RNA viruses have a substantial impact on world health and play a key role in the emergence and resurgence of infectious illnesses (34). Furthermore, they hypothesized that megatrends that are already affecting society, such as urbanization, deforestation, and climate change, will lead to the discovery of more RNA viruses and the development of new RNA viruses that have the capacity to spread like wildfire. It is now clearer that achieving the described here is a tailored product profile. may offer a helpful protection against current RNA viral threats as well as emerging RNA viruses that are going to surface from the growing (35,36).

Based on the planned target product profile and the general experience with authorized medications for viral infections, the decision was made to target the RNA-directed RNA polymerase, which is encoded by all RNA viruses (37). Because they can both duplicate genomic RNA and transcribe mRNA from genome templates, In the viral replication cycle, the RdRps are vital enzymes. Since there are no known mammalian parallels, it would be possible to target the RdRp with a high degree of selectivity. These enzymes are the most conserved proteins that RNA viruses express. In terms of structure, the RdRlmThe three conserved subdomains of the RdRps' structure—the fingers, thumb, and palm—are the typical "right hand" arrangement found in all polymerases (38,39). Important enzymes in the viral replication cycle include the RdRps because they can both replicate genomic RNA and transcribe mRNA from genome templates. The palm subdomain may have the structurally necessary RdRlmA number of conserved primary sequence motifs for catalysis. the RdRps have been proposed as the greatest target for attaining wide spectrum activity across a variety of RNA families (40).

By using RNA analogs that specifically serve as competitive alternative substrates and interfere with viral genomic and/or mRNA production when incorporated into nascent chain RNA, we decided to target the RdRp (41,42). Nucleoside analogs, which work through this mechanism, are widely considered a cornerstone of contemporary antiviral treatments, has over thirty authorized for use in the management and prevention of viral infections, either alone or in

combination. Despite the fact that there are several thorough evaluations of the discovery and advancement of these nucleoside analogs, it's crucial to highlight some key features of these drugs as antiviral agents. These characteristics significantly impact their effectiveness, particularly in addressing newly RNA viral infections, both new and reemerging, and public health issues (43,44). Additionally, nucleoside analogs are usually taken orally or can be made so using prodrug techniques, allowing self-administration in emergency scenarios where it would be necessary to treat a vital number of patients right away (45). It is necessary to note that the ribonucleoside analogue RdRp inhibitors usually work well against a variety of RNA virus families. Therefore, creating a single ribonucleoside analog as a treatment for a single RNA virus that is reemerging or emerging might lead to a countermeasure for several RNA viruses. This is the case with molnupiravir, which is why it was developed so rapidly to treat COVID-19 (46,47,48).

We started assessing ribonucleoside analogs' efficacy against alphaviruses in 2013. quickly emerged as a promising candidate with activity against both the chikungunya virus and the New World encephalitic alphaviruses. Prior to this, EIDD-1931 showed antiviral effectiveness and a good cytotoxicity profile in cell culture infection models, according to many investigations. EIDD-1931 is bioavailable when taken orally, effectively enters the central nervous system and is broadly disseminated to several organs, including the lungs, where it is quickly converted to its active 5′-triphosphate form, according to additional pharmacokinetic and distribution studies conducted in mice, rats and dogs (49,50). The pathophysiology of VEEV infection necessitates consideration of the virus's replication in the central nervous system in order to reduce death in mouse models of infection (51). A pro drug allowed for easier passage across the gut lining. Consequently, molnupiravir, EIDD-2801 emerged as a potential clinical development candidate (52,53).

A shift in clinical development goals in response to a global pandemic
In late 2019, when SARS-CoV-2 became a global health problem, an IND for molnupiravir was being prepared to treat seasonal influenza (54). This drug development pathway was selected after consulting with funding agencies that had aided in the discovery and development of EIDD-2801 (55,56). leading to its consideration as a potential countermeasure for highly pathogenic coronavirus infections. The Authority for Biomedical Advanced Research and Development launched a webpage in January 2020 to gather information on possible COVID-19 countermeasures as the outbreak worsened. Early in February, DRIVE/EIDD responded by sending a presentation and summary to BARDA. However, BARDA did not provide any feedback on our evaluation of molnupiravir as a treatment option. However, in late February 2020, we received a request from the US Food and Drug Administration for all relevant information about the effectiveness of EIDD-2801 against dangerous coronaviruses. To accelerate the initiation of a Phase 1 clinical study to assess EIDD-2801's pharmacokinetic, safety, and tolerability characteristics, we decided to file the IND for influenza as scheduled. On March 25, 2020, DRIVE filed the influenza IND (57).

We at DRIVE and the EIDD realized that more resources would be required to speed up efforts as the epidemic worsened. As a result, a licensing agreement was signed in March 2020, a biotechnology company that had just finished developing a therapeutic medication to treat Ebola infection. On April 7, 2020, Ridgeback Biotherapeutics received the IND for the treatment of influenza. Ridgeback filed a second IND on April 10, 2020, to treat illnesses caused by pathogenic coronaviruses, and on April 16, 2020, the FDA granted a safe-to-proceed

letter. Ridgeback Therapeutics quickly put up a project team with professionals from DRIVE/EIDD (58,59,60).

Numerous in vitro and in vivo studies have assessed molnupiravir's potential for genotoxicity, following a positive result in the Ames test. However, strong evidence suggesting that the Ames test may not be relevant for molnupiravir can be found in the mutagenicity assays before clinical trials can begin. These tests were created in cooperation with The Harmonization of Technical Requirements International Conference for Pharmaceutical Registration's Expert Working Group on Safety and are conducted according to established, validated protocols. It is well known that no single in vitro test can adequately evaluate genotoxicity; instead, in vivo investigations are required to determine the biological relevance and any clinical hazards that are brought to light by in vitro results. Thus, two distinct in vivo rodent mutagenicity assays were conducted, which are considered reliable and well-established, were used for further evaluation (61,62). Treatment with molnupiravir had an effect on mutation rates that was indistinguishable from that of untreated historical control animals in each assay, which was performed at significantly higher doses and durations than those used in clinical practice. Additionally, molnupiravir did not cause chromosomal damage in rat micronucleus tests. (63,64). Due to concerns regarding the infectivity status of possible healthy, normal participants and the spread of COVID-19, several clinical facilities in the United States were closed at the start of the experiment. To increase the possibility of conducting Phase 1 research uninterrupted by the potential shutdown of investigational facilities because of COVID-19, regulatory files were also made in the United Kingdom, where the impact of the virus was not as severe at the time (65,66). By comparing the influenza and coronavirus INDs, the FDA sped up the Pre-IND Meeting and review procedure (67,68). These guidelines outlined the steps to ensure timely scientific guidance, evaluation, and approval of potential treatments. The MHRA's real-time feedback enabled the project team to make necessary adjustments before formally submitting the CTA. Additionally, the MHRA advised that instead of using the standard Combined Ways of Working pathway for Research Ethics Committee (REC) applications, which allows for simultaneous regulatory and ethics review (69,70).

A Phase 1 randomized, double-blind, placebo-controlled trial with healthy volunteers examined the impact of meals on pharmacokinetics and the assessment of single and repeated doses of molnupiravir. EIDD-1931 quickly surfaced in plasma, with a median detected concentration time of 1.00 to 1.75 hours following molnupiravir injection. After many doses or larger single doses, it appeared to have a delayed elimination phase and it then decreased with a geometric half-life of around 1 hour. After many doses, there was no accumulation, The rate of absorption decreased when given in a fed condition, although there was no overall (71,72,73).

Antiviral medication mechanism of action Infectious illnesses have been recognized since the beginning of human civilization. Infectious illnesses are affected by a vital variety of microorganisms, such as bacteria and fungus. It is difficult to create drugs that are specifically detrimental to viruses because of these characteristics. Viruses are tiny creatures containing genetic material. Given that individuals and viruses will employ different tactics (74). Dynamic antiviral medication development is desperately needed, since millions of people have died from viral diseases throughout human history. A new era in the development of antiviral

medicine began in June 1963 with the approval of "idoxuridine," the first antiviral drug. Since then, Numerous medications possessing antiviral properties have been created for therapeutic use to treat millions of patients worldwide. Antiviral medicines are a class of pharmaceuticals designed to treat viral infections. Certain antiviral drugs are used to treat certain viruses, just like antibiotics are used to treat bacteria. Antiviral drugs, in contrast to the majority of antibiotics, they stop their growth. Given that the viruses need the host's cells to multiply (75,76,77).

Only a few numbers of antiviral medications are accept for use in humans because of side effects or drug resistance, even with the availability of contemporary instruments and strict quality control protocols. Growing understanding of viruses and how they infect people, The current state of the world indicates that microbial threats are continuing to increase at a rapid rate, mostly due to globalization and unanticipated climate change (78).

DNA Viruses such as papilloma, adeno, and poxviruses usually only contain single-digit DNA instead of double-stranded DNA. When a DNA virus enters the cell centre, more viruses are produced (79). Retroviruses viruses are examples of RNA viruses. All of them fall within the single descriptor RNA (ssRNA) category. This season, The RNA virus cannot penetrate the cell core, in addition to being infected by the cold virus. After being arranged by the host genome and subsequently by a retrovirus, viral RNA is utilized to create a DNA replica of the viral RNA (80).

How to prevent getting a virus As part of a viral infection, viral DNA enters a host cell, replicates there, and releases other viruses. The six steps of viral replication include attachment, invasion, uncoating, replication, assembly, and release. The stages of a virus's life cycle that show where it can enter and leave (81,82).

Drug repurposing efforts during the COVID-19 pandemic:

Safe and effective pharmaceuticals must be quickly and affordably accessible in order to improve patient health outcomes. This was especially crucial during the COVID-19 pandemic, which resulted in a large and unanticipated public health need for prompt access to effective and safe therapies for a disease for which there are presently no known cures. Despite the pressing public health needs, drug development often takes place over much longer periods of time. Developing a novel medication from preclinical research to regulatory clearance usually takes 10 years. During a pandemic of new illnesses, delays in treatment discovery can lead to significant morbidity, death (83).

Throughout the COVID-19 outbreak, drug repurposing—the practice of employing a treatment that has been authorized for one use to target another—has shown a viable means of accelerating the discovery and development of novel medications. Researchers focused on the possible cures from repurposing, even though the crisis spurred amazing attempts to quickly develop innovative medicines—most notably immunizations generated in record-breaking periods (84,85).

In general, drug repurposing offers three main advantages over the development of new drugs from scratch. First, repurposed drugs are often considered safer because they are based on medications that have already been through clinical trials and regulatory reviews, reducing the risk of exposing patients to unknown side effects. While more is typically known about

potential side effects when repurposing a drug compared to developing a new one, regulators generally assess the benefit-risk balance in drug repurposing and de novo drug development as being similar (86). A second advantage of drug repurposing is that researchers can leverage previous medication development experience to accelerate the process and reduce costs. Finally, since many repurposed drugs already have generic versions, patients may benefit from lower costs and improved access to these treatments, making pharmaceutical advancements more affordable (87).

Beyond COVID-19, repurposing offers medical and economic benefits. Drug repurposing has become more popular in recent years as a means of treating a wide range of ailments. The development of new techniques based on artificial intelligence, in silico screening, as well as new data sources like comprehensive electronic health records, may make repurposing more important in the future (88,89).

Despite the great interest, much remains to be discovered about the organizations and laws that could best support the safe, effective, rapid, and accessible repurposing of drugs. Concerns have long been that the current legal and commercial frameworks do not provide sufficient incentives for repurposing. The costs of developing new indications for drugs that are currently competing with generic versions—that is, drugs that may potentially provide the greatest economic benefit from repurposing—may be hard for pharmaceutical companies to recoup. There are additional challenges when repurposing during a pandemic, such as maintaining high scientific standards, ensuring that ethical trial design is followed, and communicating results to the public in an understandable and regular way (90).

There is currently very little empirical evidence in Favor of repurposing medications for COVID-19. The few research that has examined this has been case studies, centered more on science than policy, or was carried out at the very beginning of the epidemic. Similarly, systematic knowledge to inform medication repurposing policy generally is lacking. FDA approvals, case studies, and bibliometric data have all been used in earlier research (91,92).

We contribute to the body of current research by presenting comprehensive empirical data on the magnitude and extent of medication repurposing operations for COVID-19 utilizing the universe of US clinical trials. In order to guide policy for future emerging illnesses and to extract lessons for no pandemic repurposing policy, scientific discoveries, or the rent-seeking behaviour of companies. In this study, we examined how long medication repurposing trials lasted (93)

Drugs Used In Treatment:

NAME	**M.O.A**	**% used in covid 19 hospital**
Remdssivir	**Potent inhibitor of viral rna dependent RNA polymerase.**	**81%**

Molnupiravir	**Viral error induction during replication.**	**30%**
Paxlovid	**Protease inhibitor.**	**90%**
Bamlanivimab	**Nutralizing mabs/Entry inhibitor.**	**10%**
Imdevimad	**Nutralize SARs Cov-2 by binding to receptor binding domain of spike protein.**	**20%**
Dexamithasone	**Supressing the migration of nutrophils and decrease lymphocyte colony proliferation.**	**25%**

Study Data And Methods:

COVID-19 Trials

We used ClinicalTrials.gov and the Cortellis Clinical Trials Intelligence database to look for COVID-19 clinical trials in order to thoroughly evaluate COVID-19 clinical research activities, including both successful and unsuccessful development endeavors. The International categorization of Diseases, Ninth Revision (ICD-9) categorization system was used to group the medical diseases that were examined in each research. For our sample, we chose trials where the term "coronavirus" was used as the main condition under investigation. For each research, we employed extra data outlining trial characteristics, including the intervention, phase, and start date. In our analysis, we also utilized the sponsor as a stand-in for trial funding (94). We restricted the sample to 531 trials that were specifically designed to assess pharmacological efficacy, such as studies assessing small molecules, biologics, or combination products. Studies lacking phase status (n = 2), phase IV studies, and phase 0 trials were also excluded. Consequently, our final analytical data collection had 485 trials (95,96).

Repurposed Drugs:

To determine whether a medication under research has FDA approval, we manually examined the FDA website's authorized indications and approval dates. Similar to the studies, FDA-approved indications were categorized using ICD-9 numbers. repurposed medications got their first FDA certification date. A list of all repurposed drugs used in the trials and a schematic of the sample selection process are provided in online appendix exhibits 1 and 2. To understand how market exclusivity and competitive dynamics contribute to the promotion of medical

repurposing, As of January 1, 2020, we manually determined if each repurposed medication had any generic competition in the US market (97).

Limitations:

First, as mentioned earlier, we focused on interventional studies in which coronavirus was the primary condition. Observational studies without a supporting trial or other factors that are closely associated with COVID-19 may be excluded. For example, in our final sample of 485 clinical trials, over 2% additionally evaluated children for multisystem inflammatory syndrome, a condition closely linked to COVID-19 (98,99).

Remdesivir, which was first created to treat Ebola but was not FDA-approved prior to the COVID-19 pandemic, is an also known example of this. Our data comprised 16 drugs that had previously received FDA clearance. Additionally, drugs that may have been previously developed, such as those having past clinical trials, were not included in our definition of drug repurposing. Without FDA clearance, a phase III investigation was carried out to test against COVID-19 prior to the pandemic. There are notable distinctions, even though many policy concerns for these "recycled" pharmaceuticals will be the same as those for repurposed drugs that have already received FDA approval. These include the amount of testing that has been done in the past and the level of business incentive to look for new indications (100).

Third, there are limitations to our study's capacity to impact the extent to which drug policy should promote repurposing. While repurposed drugs have been extremely beneficial to COVID-19 patients, we were not aware of the costs of these development efforts. As a result, even while some of the therapies being considered for repurposing had strong scientific arguments for examining their use in COVID-19, others were seen to have far weaker scientific arguments or to be on the verge of pseudoscience (101). Finally, our study looked into COVID-19 repurposing at a particular moment in time. Eventually, some of the repurposed therapies now under development may be found. Finally, our study looked into COVID-19 repurposing at a particular moment in time. While certain repurposed treatments under development may eventually prove to be useful, some presently recommended medications may show less promise when more study evaluates their use. Three years after the pandemic started, enough knowledge about the virus has been acquired to contemplate possible lessons (102,103).

Study Results:

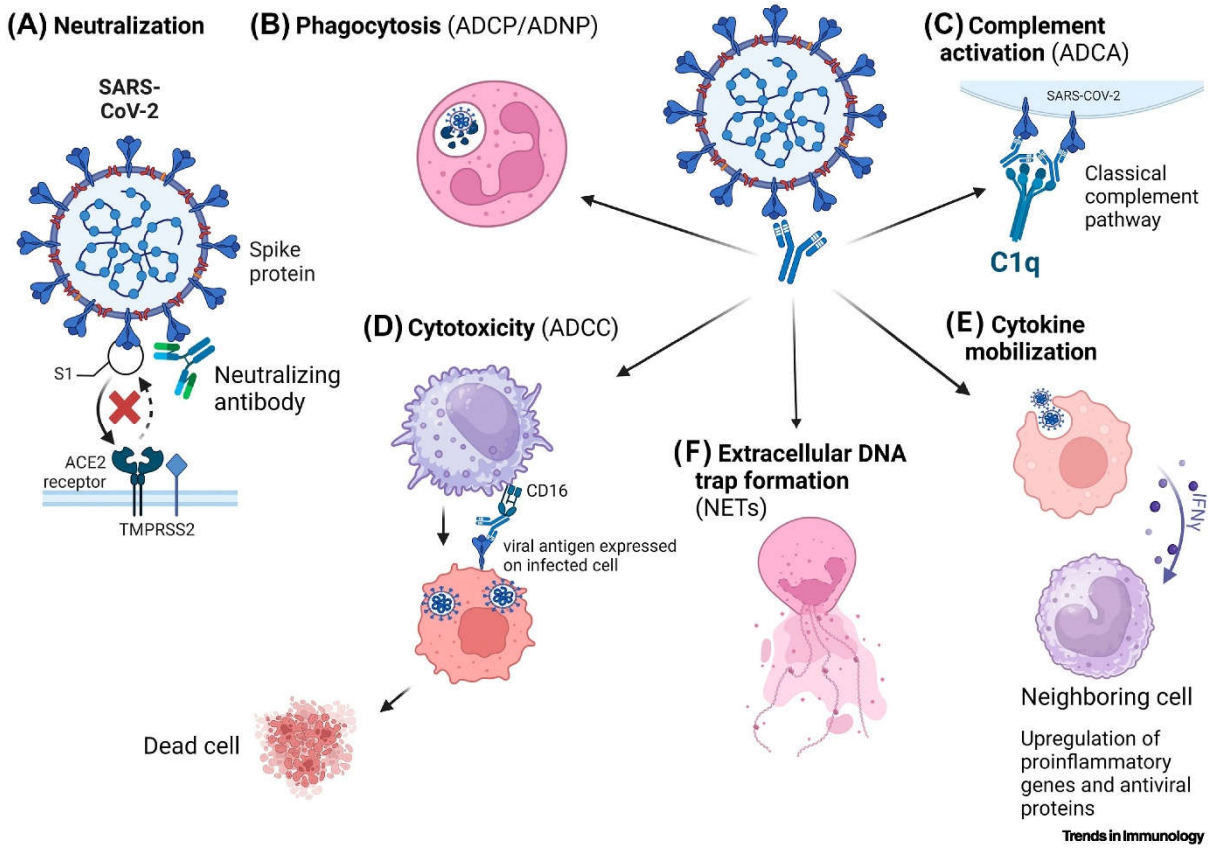
Our final analytical sample consisted of 485 clinical trials, of which 211 trials (44 percent) examined at least one repurposed medicine, for a total of 101 different repurposed pharmaceuticals assessed.

Time Course Of Drug Repurposing:

Only a few studies started in the first quarter of 2020, but the majority of trials started in the second quarter, which was the first full quarter following the WHO's declaration of COVID-19 as a pandemic. Each quarter after that, the total number of trials decreased: by the fourth quarter of 2021, there were just 31 trials, down from 154 in the second quarter of 2020. As the pandemic developed, a larger percentage of studies evaluated de novo drugs, while the majority of COVID-19 investigations first investigated repurposed pharmaceuticals. In the first half of 2020, over two-thirds of COVID-19 studies looked at a repurposed drug.

Monoclonal antibodies targeting SARS-CoV-2

FIG:1.1(104).



Antiviral Drug Resistance: Mechanisms and Clinical Implications

One of the biggest obstacles to treating patients with chronic hepatitis B is antiviral medication resistance. The use of an antiviral agent or combination of antiviral medications that is potent enough to halt viral replication and, as a result, Liver disease frequently progresses in hepatitis B patients who acquire treatment resistance, and if hepatic reserve is compromised, there may be a significant decline in clinical status. Currently, the viral reverse transcriptase (rt) has two main patterns of resistance mutations that may be chosen for monotherapy: those that include the codon rtM204, which is a component of the enzyme's catalytic domain (YMDD), and those that do not (105,106). The resistance profiles for entecavir and the tenofovir-lamivudine combination also contain it. However, mutations involving rtN236T ± rtA181V are associated with resistance to adefovir. A feasible clinical goal is to develop a comprehensive strategy that prevents resistance from being chosen for. These strategies may include a combination of medicines, however they have not yet been improved for hepatitis B. Future therapeutic approaches can be modeled after very successful anti-retroviral medication regimens created to effectively treat patients suffering from the human immunodeficiency virus (107).

Use of Artificial Intelligence and machine learning in drug discovery CRISPR-based antiviral therapies

By allowing researchers to precisely and efficiently modify genomic components, The editing of genomic targets was completely transformed by the discovery of the CRISPR/CRISPR-associated protein 9 (Cas9) system as a genome-editing tool combination. The bacterial genome initially revealed the CRISPR/Cas9 system as part of an antiviral defensive mechanism against bacteriophages. Later, it was acknowledged as a ground-breaking genome-editing technique that allowed for the insertion, deletion, and removal of preexisting genes with remarkable accuracy and specificity. (108,109).

Numerous genes have been discovered to be connected to the development and spread of cancer in recent decades thanks to high-throughput screening techniques including whole-genome, exome, and transcriptome sequencing as well as next-generation sequencing (NGS). CRISPR/Cas9 is the tool of choice for high-throughput screening methods and for investigating the function of specific genes. The data generated by these high-throughput technologies has to be verified and validated using genetic models in order to identify pharmacological targets and develop efficacious therapies. In this sense, CRISPR/Cas9 has emerged as the go-to technique for investigating the control and functionality of those genes in practical genetic models that have a similar genetic background, such as isogenic cells (110). In addition to testing and confirming pharmacological targets, CRISPR/Cas9 has shown promise when used in concert with sequencing technologies to find functional genes, such as tumor suppressors, Understanding the onset and progression of cancer is essential for developing precise therapies, and this will help us achieve that goal. A crucial step in the drug development process that contributes to the success of clinical therapy is validating the therapeutic target. Early treatment target validation enables a better understanding of how target modification affects disease biomarkers, sickness endpoints. In order to engage and confirm pharmacological targets (111).

FUTURE DIRECTIONS IN ANTIVIRAL THERAPY:

Antiviral therapy multiple viruses within a family or even across families. Unlike current drugs, which often focus on virus-specific mechanisms, broad- spectrum antivirals would address conserved viral proteins or host pathways critical for viral replication. This approach could enhance preparedness for emerging infections like those caused by zoonotic viruses. Furthermore, advancement in computational biology and machine learning are accelerating drug discovery by enabling the rapid identification of novel antiviral targets and the optimization of drug candidates. (112,113).

Gene-editing technologies, such as CRISPR-Cas systems, are also transforming the field by offering potential treatment techniques that directly destroy viral genomes. This approach has the greatest promise when traditional therapies fail to treat latent illnesses like HIV and herpesviruses. Similarly, RNA-based treatments, including antisense oligonucleotides and small interfering RNA (siRNA), are gaining popularity as ways to stop viral genes from being expressed. The stability and targeting of these molecules are being improved by advancements in delivery techniques, such as lipid nanoparticles, which are eliminating significant barriers to

their application in medicine. Another novel strategy is the use of therapeutic vaccines and immunomodulatory drugs to boost the host immune system (114,115).

The integration of nanotechnology into antiviral therapy offers innovative solutions for drug delivery and targeting. Additionally, combination therapies using nanoparticles to co-deliver multiple drugs with complementary mechanisms of action are showing promise in overcoming antiviral resistance. Developing antivirals with higher barriers to resistance, such as those that target multiple viral components simultaneously ,is crucial for ensuring long-term efficacy. (116,117).

Lastly, public health considerations are influencing the advancement of antiviral medication. The COVID-19 pandemic has demonstrated the significance of rapid-response systems that can develop new antivirals and vaccines in record time. It is likely that similar approaches for the development of antiviral medications will be influenced by advancements such as mRNA vaccine technology, which demonstrated unprecedented speed and scalability. International collaboration and equitable access to antiviral treatments are increasingly becoming important research and policy tenets in order to address disparities in healthcare access and ensure preparedness for future pandemics. Ultimately, the future of antiviral medicine lies at the intersection of cutting-edge technology, research, and global health objectives, paving the way for a more effective and resilient response to viral diseases (118,119).

Conclusion:

The creation of novel antiviral medications, especially in reaction to the COVID-19 pandemic, has led to groundbreaking advancements and shifted treatment paradigms. One key change has been the acceleration of drug repurposing efforts, highlighting the value of adaptable therapeutic strategies that leverage existing antiviral drugs and other medications for rapid deployment against SARS-CoV-2. Simultaneously, the pandemic underscored the potential of innovative platforms like mRNA technology, which has played a critical role in both vaccine development and the creation of targeted antiviral treatments. RNA-based approaches have shown promise in directly targeting viral RNA to inhibit replication, paving the way for next-generation antiviral therapies. Furthermore, because monoclonal antibody treatments offer incredibly potent and precise means of neutralizing the virus, particularly in high-risk populations, they have grown in popularity. Together with these targeted approaches, broad-spectrum antivirals that interfere with conserved viral activities or exploit host-cell pathways crucial to viral replication have garnered a lot of attention and appear to be promising in the fight against both current and new viral threats. Furthermore, computer methods, artificial intelligence, and machine learning have become increasingly important in drug development since they allow for the rapid discovery of potential antiviral agents and the enhancement of their pharmacological profiles. These advancements underline how crucial it is to create robust, egalitarian, and scalable antiviral development pipelines that can respond swiftly to emerging viruses, with a focus on pandemic preparation, as the world evolves. In order to combat viral diseases and enhance global health security, new antiviral agents will be developed in the future with unprecedented speed and precision thanks to the therapeutic landscape left behind by COVID-19, which is proof of the synergistic potential of science, technology, and international cooperation (120,121,122).

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