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The Potential of Drug Repurposing as a Rapid Response Strategy in COVID-19 Therapeutics

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Drug repurposing has emerged as a promising strategy in the rapid development of effective therapeutics for COVID-19. This approach leverages existing medications, previously approved for other indications, to target the pathophysiological mechanisms of SARS-CoV-2 infection. Several drugs were tested during the COVID-19 pandemic, developed originally for other purposes and under less-than-ideal conditions. Some of the most well-known include remdesivir, an Ebola drug approved by the FDA for emergency use to treat COVID-19, and dexamethasone, a corticosteroid that reduces death associated with severe infection through immunomodulation. However, while hydroxychloroquine and ivermectin, among others, showed very meager or no benefit, it is clear that such early promise must be subjected to firm testing. Despite such promises, drug repurposing may face several inconsistent clinical outcomes, questions over safety, and the inability to address

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all forms of COVID-19 pathology. Key candidates identified through high-throughput screening and computational methods include antiviral agents, anti-inflammatory drugs, and those targeting host cell pathways critical for viral replication. This review discusses the efficacy and mechanisms of these repurposed drugs, highlights ongoing clinical trials, and addresses challenges such as resistance and optimal dosing. Ultimately, drug repurposing represents a crucial component of the multi-faceted response required to combat the COVID-19 pandemic effectively.

Keywords: COVID-19; drug repurposing; drug repurposing techniques; drug discovery; drug repurposing approaches.

1. INTRODUCTION

The coronavirus disease pandemic of 2019 (COVID-19) has posed a serious threat to public health around the globe. The severe acute respiratory syndrome coronavirus II (SARS-CoV-II) that causes COVID-19 was first discovered and identified in December 2019 in patients exposed to a seafood market in Wuhan City, Hubei Province, China. Comparable to discoveries about SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-II is thought to commence primary human infections by cross-species transmission; at this point, it is mainly transmitted from person to person [1]. The COVID-19 pandemic has been significantly more severe even though the case fatality rate (estimated at 2%–3%) is lower than that of SARS (about 10%) and MERS (nearly 40%) [2]. As of March 15, 2020, SARS-CoV-2 infection has been detected in 144 countries, territories, and places scattered over five continents [3]. It has swiftly expanded to 34 provinces and cities in China. The COVID-19 pandemic poses a significant risk to individuals, governments, and society at large [4].

2. DRUG REPURPOSING TECHNIQUE

The process of employing an already-approved medication or medication candidate for a novel medical ailment or treatment for which it was not previously recommended is known as "drug repurposing." It was first created to address a distinct medical issue [7]. It has been characterized as an unforeseen, serendipitous procedure. In this procedure, a drug's unwanted side effects may also serve as a due to investigate whether it might be useful for a completely unrelated medical problem [8]. Typically, medications have been shown safe for use in people and tested and developed for their usefulness in treating diseases other than the one for which they were intended. By bypassing the drug development process and going straight to preclinical and clinical trials, this approach lowers the risk and costs associated with drug development [9].

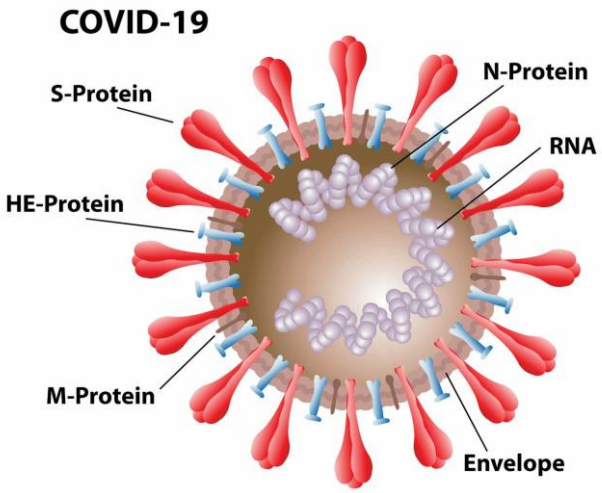

Fig. 1. COVID-19 structure with spike proteins [5,6].

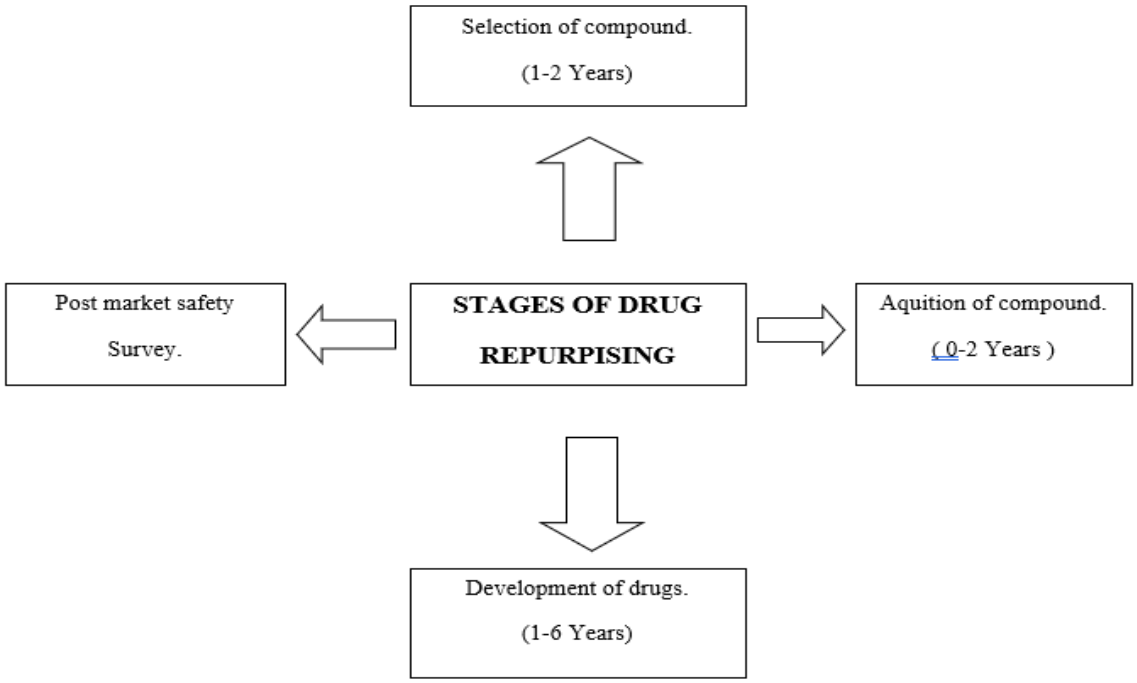

Fig. 2. Stages of drug repurposing [10]

3. SIGNIFICANCE OF DRUG REPURPOSING

New drugs must meet strict standards before entering the market. Identifying and developing a medicine involves significant investment due to its numerous physicochemical features and the challenge of scaling up production. This constraint allows pharmaceutical companies and research organizations to efficiently use licensed drugs for new indications that are not yet available to individuals with the condition [11]. Molecules that do not exhibit efficacy for a certain indication can be repurposed for further research. They can be rediscovered for new indications and developed into viable medicines, especially for rare diseases that face major challenges in diagnosis, therapy, and limited resources [12]. Idiopathic conditions, such as autoimmune illnesses, bacterial infections, and uncommon malignancies, can be challenging to treat as they are not inherited. Drug repurposing is a cost-efficient and time-saving alternative to standard discovery and development processes, resulting in beneficial medications for patients. This technique reduces drug development costs, lowering patients' out-of-pocket expenses and therapy costs [13]. New experimental molecules lack safety and efficacy data, leading to higher attrition during the drug discovery process and increased failure rates. In comparison, all safety, preclinical, and effectiveness data. The availability of repurposed molecules allows for informed decision-making at each stage of therapeutic development. Prior knowledge of a drug's safety, efficacy, and delivery route can significantly reduce development costs and time, leading to a more successful market launch. Sildenafil, a PDE5 inhibitor, is an example of successful repurposing efforts. Sildenafil was initially intended to treat hypertension but has now been approved by the FDA for erectile dysfunction due to its great benefits [14]. It was eventually repurposed to treat a rare condition, pulmonary hypertension. New technology and computational methods have made drug discovery more cost-effective, especially when starting with an approved medicine. In recent years, this method has been responsible for approximately 30% of new FDA-approved medications. Drug repositioning has a high potential for out-licensing due to appealing attributes for potential buyers [15]. Identifying a new disease target should not negatively impact the drug's marketing prospects for its initial indication. Rare illnesses pose a significant unmet medical need due to the lack of traditional medicines and poor clinical outcomes, making

medication repurposing a key area of research that outlines the fundamental differences and benefits of drug repurposing approaches over traditional drug discovery approaches [16].

4. COVID-19 DRUG REPURPOSING RESEARCH

A global public health disaster resulted from the introduction of the novel severe acute respiratory syndrome coronavirus-II (SARSCoV-II). The coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-II, which was initially discovered during a SARS outbreak in the Chinese province of Wuhan in December 2019 [18]. The World Health Organisation (WHO) proclaimed a pandemic in March 2020 due to the rapid spread of COVID-19 to multiple countries and almost every continent. As of February 2022, there have been over 400 million confirmed cases and 5.8 million deaths of the virus documented globally. In many places of the world right now, the situation is still completely out of control. Large, enclosed, positive-sense, single-stranded RNA viruses known as coronaviruses have been reported to infect a variety of animal taxa, including birds, mammals, and reptiles [19]. It is well known that coronaviruses can "jump" between species on occasion and modify themselves to fit in with their new host, just like other viruses can. Recent examples of coronaviruses that were previously believed to be restricted to their natural host reservoirs—bats—that have evolved to infect and replicate in humans include the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV). However, dromedary camels and civets, respectively, served as intermediate hosts in the zoonotic transmission of MERS and SARS-CoV to humans, rather than a direct route. Like MERS-CoV and SARS-CoV, it's possible that SARS-CoV-II originated from a zoonotic agent. Although bats are most likely the source as well, an intermediary host could not be definitively established [20]. The main way that SARS-CoV-2 is spread is by direct contact with respiratory virus-containing aerosols and droplets from sick people. Sneezing, coughing, and nasal discharge are common ways to spread infection. The discovery of SARS-CoV-2 genetic material in several organs, however, suggests that the tropism is not limited to the upper and lower respiratory tracts. This could be partially explained by the expression of angiotensin-converting enzyme 2 (ACE-II), the primary cellular receptor for SARS-CoV-II, in several human tissues and organs. The most typical COVID-19 symptoms include dyspnoea, tiredness, fever, and cough. Nonetheless, patients and people recovering from convalescence have been found to have impairments in numerous organ functions, including neurological, cardiac, hepatic, and kidney. The disease's outcome can be fatal, most frequently as a result of severe viral pneumonia symptoms that primarily affect the elderly and those with compromised immune systems. Furthermore, it is believed that the existence of additional concurrent clinical disorders, such as diabetes and chronic heart disease, may potentially be a significant risk factor influencing the course of the illness [21].

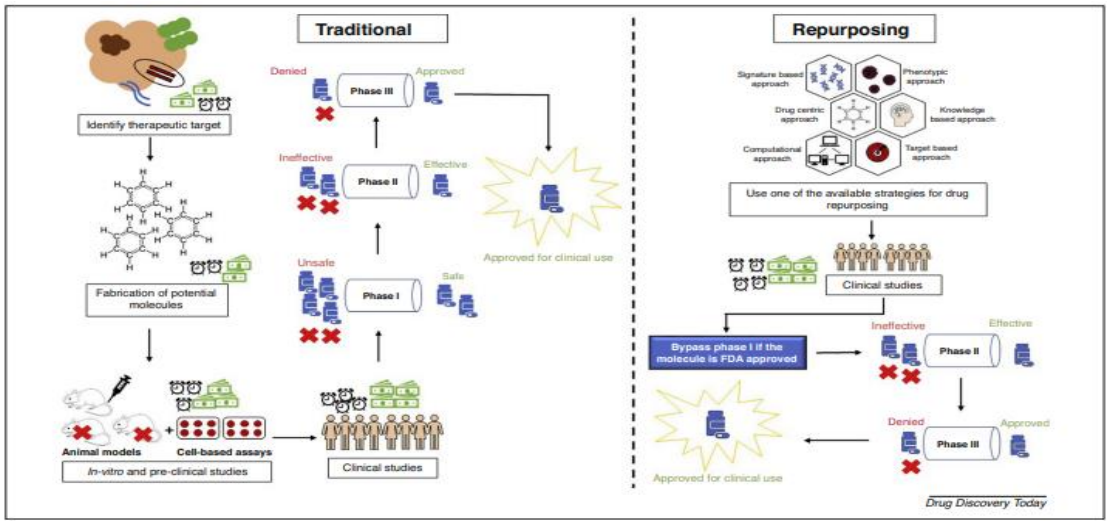

Fig. 3. Drug discovery today [17]

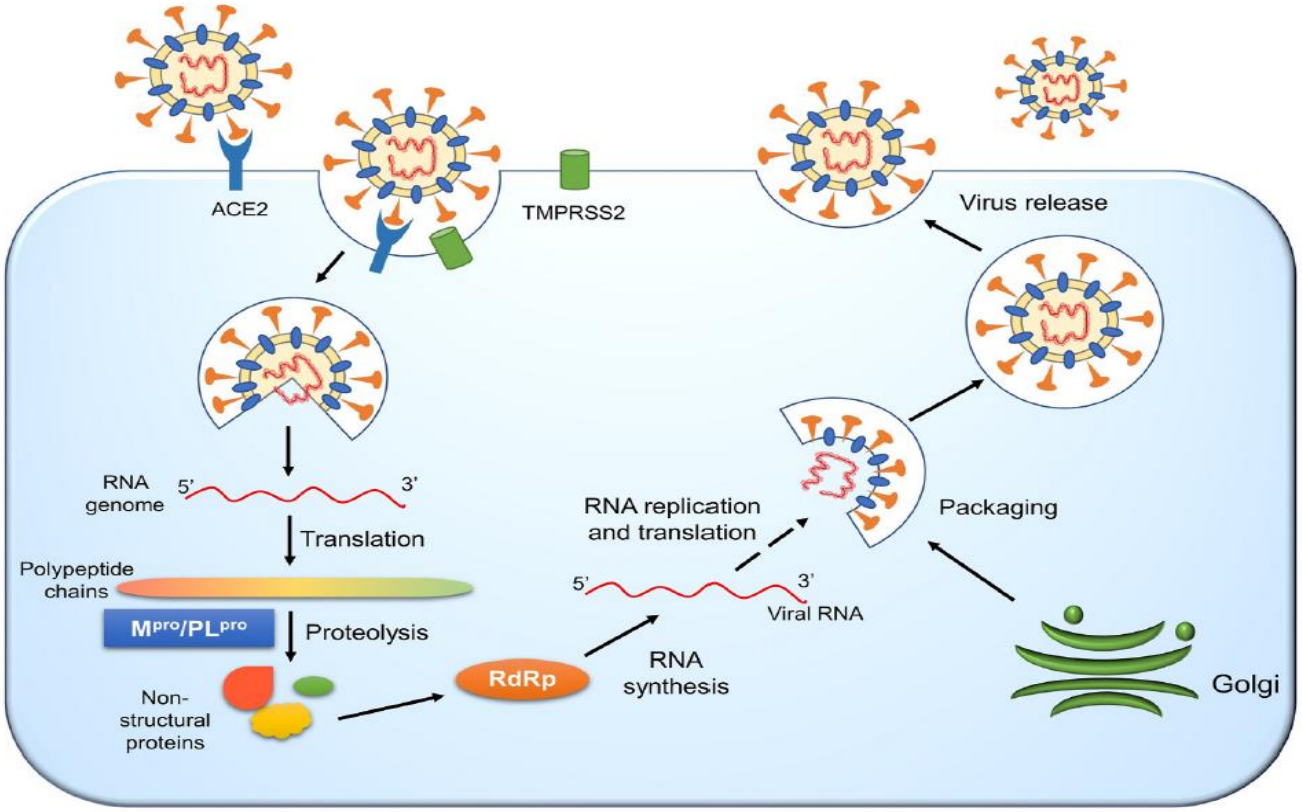

Fig. 4. Schematic diagram of life cycle of SARS-CoV-2 [22,6]

Table 1. Examples of repurposed drug

Sr.no.	Drug	Discovered	Repurposed	Reference
1.	Amiloride	Acid-sensing ion channel antagonist	Secondary progressive multiple sclerosis (SPMS)	[24]
2.	Aspirin and ibuprofen	Inflammation	Antibacterial and antifungal	[25]
3.	. Bleomycin	Antitumor	Active against fungal biofilm	[26]
4.	Cyclosporine	Anti-inflammatory /Immunomodulatory	Active against fungal biofilms	[27]
5.	. Daunorubicin	Acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and Kaposi's sarcoma	Antibacterial and antifungal	[25]
6.	Diazepam	Antipsychotic/Antidepressant	Active against fungal biofilms	[28]
7.	. Digoxin	Treatment for cardiac diseases	Anticancer	[29]
8.	Dihydroartemisinin	Anti-infective	Active against fungal biofilms	[16]
9.	Doxorubicin	Antibiotics from Streptomyces peucetius bacterium,	Bladder, breast, stomach, lung, ovarian, and thyroid cancers	[14]
10.	Ebastine	Anti-inflammatory/Immunomodulatory	Active against fungal biofilms	[30]
11.	Fluorouracil	Keratoacanthomas, actinic keratosis, and skin warts\/	Breast cancer	[31]
12.	Fluoxetine	Antipsychotic/Antidepressant, Serotonin selective reuptake inhibitor (S	Active against fungal biofilms, secondary progressive multiple sclerosis (SPMS)	[9]
13.	Fluvastatin	Lipid-lowering	Active against fungal biofilms	[32]
14.	Fulvestrant	Antiestrogen	Breast cancer	[33]
15.	Human Albumin	Blood additive	Immuno-restoration	[29]
16.	Itraconazole	Antifungal	Anticancer	[25]
17.	Ivermectin	Ivermectin	Effective against SARS-CoV-2 (COVID-19) [safe in conventional doses]	[34]
18.	Losartan	Blood pressure reduction	Alzheimer's disease, Treatment of Covid-19	[29]
19.	Mebendazole	Antiparasitic/Helminthiasis/ Antinfective	Brain cancer (i.e.,medulloblasto a and glioblastoma)/Anti acterialand,	[33]
20.	Metformin	Diabetes	Anti-cancer, and augmented resistance in aging, Colo rectal cancer	[35]
21.	Methotrexate	Leukemia	Breast cancer	[36]
22.	Midazolam	Antipsychotic/Antidepressant	Active against fungal biofilms	[14]

23.	Niclosamide	Helminthiasis/Anti-infective	Antibacterial and antifungal and active against fungal biofilms	[13]
24.	Nitroxoline	Anti-infective	Active against fungal biofilms	[27]
25.	Oxyclozanide	Helminthiasis	Antibacterial and antifungal	[25]
26.	Phenobarbitone	Anticonvulsant	Active against fungal biofilms	[29]
27.	Propanolol	Antiarrhythmic	Active against fungal biofilms	[9]
28.	Ribavirin	Antiviral drug	Effective against SARS-CoV-2(COVID19)	[13]
29.	Rifampicin	Anti-infective	Active against fungal biofilms	[9]
30.	Sildenafil (Viagra)	Angina	Erectile dysfunction,	[36]
31.	Sulfadiazine	Anti-infective	Active against fungal biofilms	[15]
32.	Telmisartan	Blood pressure reduction	Abdominal aortic aneurysm	[37]
33.	Thiotepa	Immunosuppressant	Breast cancer	[34]
34.	Valproic acid	Anticonvulsant	Active against fungal biofilms	[38]
35.	Vinblastine	Hodgkin lymphoma, non-Hodgkin’s lymphoma, hist	Breast cancer	[9]
36.	Yohimbine hydrochloride	Vasodilator	Active against fungal Biofilms	[29]

Table 2. Approaches to drug repurposing [41]

01	02	03	04	05
Machine Learning	**Genetic Association**	**Structure-based**	**Pathway-based**	**Artificial Intelligence**
Systematic analysis of drug, omics, and patient data using deep learning and neural network algorithms to generate novel and repurposable SARS-CoV-2 targets	Identification of genes associated with other viral diseases to generate a list of potential therapeutic targets against SARS-CoV-2	Computationally Predict the binding complementarily of a known drug to novel therapeutic targets.	Network analysis of genetic protein and disease data to identify useful repurposing candidates against SARS-CoV-2	Analyse and perform drug searches from an enormous amount of textual data to extract hidden patterns and discover putative SARS-CoV-2 drug candidates.

Worldwide, humans are frequently afflicted by seasonal coronaviruses, which typically result in a minor respiratory illness. The development of a particular antiviral medication or prophylactic vaccination was not seen as a priority since they are not acknowledged as posing a significant threat to public health. Consequently, there were no particular antiviral therapies for coronavirus disorders, such as COVID-19, when SARS-CoV-2 first appeared. The process of developing new therapy alternatives and identifying novel targeted anti-viral drugs using classical methodologies is a laborious and intricate one that can span multiple years. Within this framework, drug repositioning has surfaced as a potentially beneficial and promising method to find medications that are already licensed for use in treating other illnesses, such as COVID-19. The availability of data regarding the pharmacokinetics, pharmacodynamics, and toxicity of a particular medicine of interest is one of the primary benefits of drug repositioning. The time it takes to discover a COVID-19 medication that works might be greatly shortened by employing comparable techniques to uncover anti-SARS-CoV-II compounds. This would lower the illness burden, including the amount of hospital admissions, fatalities, and long-term consequences [23].

5. DRUG REPURPOSING APPROACHES

Before being taken into consideration for advancement through the development pipeline, drug repurposing for COVID-19, like all other drug repurposing projects, must pass three stages: identification of potential candidates for use as drugs; mechanistic assessment of the drug effect in preclinical models; and assessment of potential drugs' efficacy in phase II clinical trials. The most important of these three processes is the first one, which is to find a COVID-19 medication with a high potential for repurposing. This will determine whether the candidate drug is successful in repurposing. As a result, selecting the appropriate medication with great confidence usually involves using a methodical approach [39].

The two main categories of the systematic approach to drug repurposing are computational and experimental, though it's important to remember that these methods can work in concert to produce the greatest repurposing results [40].

6. COMPUTATIONAL APPROACHES

6.1 Machine Learning Based

In general, computational methods make extensive use of machine learning to extract dependencies from exponentially vast amounts of biological data. Novel drug repurposing hypotheses against SARS-CoV-2 will then be derived by the systematic examination of omics (e.g., genomics, transcriptomics, proteomics, metabolomics) data, chemical structure, molecular docking studies, and previous SARS-CoV and MERS-CoV clinical data. Researchers use a range of machine learning (ML)-based approaches, including deep learning and neural networks, to find repurposable candidates in drug repurposing [42].

Several deep-learning methods have been created during this pandemic to find new drug-protein interactions. One such approach is the molecular transformer-drug target interaction (MT-DTI), a deep-learning model intended to

predict the affinity of drug-protein binding. With a dissociation constant of 94.94 nM, atazanavir is a promising inhibitor against SARS-CoV-2 3C-like proteinase, as demonstrated by Beck and colleagues using this model. In a different study, an integrative method called CoV-KGE—which combines network-based and deep learning approaches—has discovered 41 repurposable medications, some of which have been verified by transcriptomics and proteomics data obtained from ongoing clinical studies. Virtual screening and supervised machine learning techniques have been used to identify novel medicines, such as the anti-HCV drug IDX-184, for SARSCoV-2 in addition to currently licensed medications [43].

To create a graph neural network for the treatment of COVID-19, different biomedical entities (such as drugs, proteins, and diseases) are represented by nodes, and the relationships between the entities are represented by edges (such as interactions between diseases and proteins). Using this method, Hsieh and colleagues have published a streamlined medicine repurposing approach that uses deep graph neural networks and SARS-CoV-2-drug interactions to rank the most promising repurposing options. Since then, 22 different medications and pharmacological combinations have been effective in treating COVID-19 [44].

ML-based drug repurposing has a limitation. Researchers need to use multiple sources of data to generate reliable predictions of repurposable candidates. The type and quantity of datasets used in computational drug repurposing can significantly impact the results. Due to the recent emergence and ongoing evolution of COVID-19, there is currently no consensus on the type of patient information that should be used to predict and screen drug candidates. As a result, different research groups report subsets of potential repurposing candidates. Researchers must develop an efficient ML-based repurposing algorithm that can adapt and respond to future disease outbreaks by utilizing standardized patient information [45].

6.2 Genetic Associations

In the last ten years, the rise of genome-wide association studies (GWAS) has enhanced our comprehension of the pathogenesis of numerous infectious diseases and the genetic variations linked to them. As biological data becomes more accessible, it is now feasible to pinpoint new targets for existing drugs to treat disease traits identified by GWAS, leading to drug repurposing. Significant advancements have been achieved in understanding the genetic elements contributing to the development of COVID-19 through GWAS. The Severe Covid-19 GWAS Group conducted a study involving 1980 severely ill COVID-19 patients, which pinpointed the 3p21.31 gene cluster as a genetic susceptibility locus in COVID-19 patients with respiratory failure. The gene cluster at 3p21.31 includes the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1, which could potentially serve as new targets for drug development for COVID-19 [46].The GWAS study has revealed multiple repurposing opportunities, but the main challenge with GWAS, not just about COVID-19, is the vast amount of data it produces, leading to the discovery of numerous associations that need validation through alternative methods. Moreover, GWAS heavily relies on the availability of an adequate number of genomes for analysis to address the issue of multiple testing, necessitating collaboration among clinicians and researchers in COVID-19 hotspots due to restricted travel during the pandemic. An additional significant issue regarding the credibility of GWAS is the problem of population stratification, with most GWAS signals being linked to concealed population stratification. To address this issue, researchers should consider using family-based GWAS or implementing adjustments for the population substructure. Therefore, although GWAS is effective in pinpointing genetic factors associated with COVID-19, researchers should use GWAS judiciously and carry out additional functional studies to establish the impact direction (agonist or antagonist) of the gene variant before predicting repurposing targets [47].

6.3 Structure-based

One of the most widely utilized strategies for drug repurposing during the COVID-19 pandemic has been structure-based screening studies aimed at identifying inhibitors for SARS-CoV-2. Numerous research groups globally have reported significant findings in this area, facilitated by advanced computational capabilities and the accessibility of three-dimensional structures of both drugs and receptor targets. Structure-based screening serves as a computational methodology employed in the initial phases of a drug repurposing initiative, allowing for the examination of a library of compounds to identify

bioactive molecules that interact with a specific drug target, based on the compatibility of binding sites [48]. This virtual screening process unfolds in two distinct phases. Initially, molecular docking is conducted on a selection of drug candidates to assess their binding potential to the three-dimensional structure of a molecular target, which may be derived from NMR, X-ray crystallography, or computational modeling. Subsequently, a scoring function is utilized to estimate the probability of each ligand binding to the molecular target with a high degree of affinity, thereby yielding promising candidates for repurposing [49].

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The target-centric strategy proves to be particularly beneficial in the context of SARS-CoV-2, as there exists a substantial understanding of its predecessors, SARS-CoV and MERS-CoV, along with their cellular targets. This prior knowledge may eliminate the necessity to clarify the mechanisms of action for the identified compounds. Consequently, numerous drugs can be evaluated against a specific target, such as Angiotensin-Converting Enzyme 2 (ACE2), similar to traditional docking methods. For instance, Elfiky employed standard molecular docking techniques focusing on the RNA-dependent RNA polymerase (RdRP) of SARS-CoV-2 to identify potential inhibitors. His research screened various approved anti-polymerase medications, revealing ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir as effective RdRP inhibitors, with binding energies ranging from −7.0 to −7.8 kcal/mol. On the other hand, a drug-centric approach can also be utilized to discover novel interactions that may yield new insights into COVID-19. An illustration of this antiviral target-based, drug-centric method is provided by Martin and Cheng (2020), who initially recognized toremifene as a promising drug candidate for SARS-CoV-2, subsequently conducting molecular docking to ascertain the molecular targets of toremifene. They successfully pinpointed two potential targets: the spike glycoprotein and NSP14 [10].

6.4 Pathway Based

Pathway mapping has emerged as a fundamental element in the repurposing of drugs during the ongoing pandemic. This methodology serves as an essential complement to Genome-Wide Association Studies (GWAS) data, as the gene targets identified through GWAS may not always be suitable for drug targeting. In such cases, conducting a pathway analysis of the genes that are either upstream or downstream of a GWAS-associated target can facilitate the identification of promising candidate drugs for repurposing [51].

In the process of pathway mapping, various types of information, including gene expression data, protein interactions, and metabolic pathways, are utilized to create networks that link drugs and diseases. This enables the identification of lead targets for drug repurposing based on shared molecular mechanisms. Through network proximity analyses that examine the relationships between drug targets and interactions with HCoV-host in the interactome, Zhou and colleagues successfully identified 16 potential drugs for repurposing, such as sirolimus, irbesartan, and melatonin [52].

However, it is important to acknowledge the limitations associated with pathway mapping. A significant drawback is the reliance of these methods on the gene annotations that are currently available in databases. The completeness of gene annotations remains inadequate, with numerous genes still unannotated and many others requiring updates as new experimental data becomes available. A

considerable number of these annotations necessitate manual curation, indicating that a comprehensive annotation of human genes is unlikely to be achieved shortly. Consequently, the incomplete nature of human gene annotations may hinder pathway mapping's ability to fully delineate the gene interactions between the target gene and its upstream and downstream effectors, potentially overlooking critical genes that could serve as viable drug targets [53].

6.5 Artificial Intelligence (Ai) Based

In the current era characterized by vast amounts of data, the application of artificial intelligence (AI) in drug repurposing has gained significant attention globally, particularly during the pandemic. This surge in interest is attributed to the exceptional computational capabilities of AI models and algorithms, which facilitate the analysis and processing of extensive datasets related to infectious diseases and public health surveillance. Consequently, researchers are increasingly utilizing this technology to extract valuable insights from millions of patient records and clinical trial data, employing various AI methodologies, including deep learning architectures and graph representation learning [54].

International research initiatives are actively exploring AI-driven drug repurposing strategies for COVID-19, exemplified by the establishment of web servers and resources such as the CLAIRE Innovation Network. Although AI-based drug repurposing is still in its early stages, preliminary findings have been promising. For instance, utilizing BenevolentAI's knowledge graph, Richardson and colleagues successfully identified baricitinib as a potential treatment for SARS-CoV-2 from an existing list of approved medications. Additionally, an AI platform developed by Ke and associates has predicted over 80 potential drug candidates for repurposing, with eight of these drugs validated for their in vitro antiviral activity against the feline infectious peritonitis (FIP) virus in Fcwf-4 cells. Furthermore, AI can be integrated with other computational techniques to expedite the screening process of drug libraries. For example, two independent studies employed AI alongside molecular docking to identify potential therapeutic agents against COVID-19 [55].

The findings presented herein, while promising, have revealed distinct challenges due to the initial scarcity of training data at the onset of the COVID-19 pandemic. This limitation has hindered the development of precise predictive AI algorithms at a time when disease forecasting and drug screening are of utmost importance. Additionally, existing AI-driven tools predominantly focus on a single type of data. Given the intricate nature of COVID-19, relying on a singular data source for AI-based predictions may lead to an inaccurate representation of the potential efficacy of drug repurposing candidates. This situation underscores the necessity for the advancement of more sophisticated AI tools in drug repurposing that can integrate diverse and multimodal data, thereby enabling researchers to make well-supported decisions regarding drug repurposing. In this regard, the Multimodal Restricted Boltzmann Machine (MM-RBM) approach has been identified as a promising method for linking various modalities in drug repurposing applications [56].

6.6 Covid-19 Drug Repurposing Candidates

Numerous COVID-19 clinical trials are presently in progress to ascertain the potential for repurposing clinically authorized medications. As of May 8, 2021, there were 5619 registered clinical trials for COVID-19, including investigations on repurposing, vaccination, and medication safety assessment. The majority of the medications under evaluation for repurposing fall into one of three main categories: 1) block one or more CoV replication cycle stages; 2) mitigate the effects of SARS-CoV-2 infection; or 3) mitigate the effects of COVID-19 infection indirectly by tampering with cellular immune and metabolic pathways [57].

7. DRUGS INHIBITING REPLICATION CYCLE OF SARS-COV-2

7.1 Virus Attachment and Entry into Host Cell

Often, the first targetable stage in any virus reproduction cycle is to inhibit the virus's ability to enter host cells. The binding relationship of the CoV spike (S) protein to the transmembrane protease serine 2 (TMPRSS2) and ACE2 receptor on the target cell, as well as endocytosis, enhances the entry of SARS-CoV-2 into host cells. Therefore, substances that may affect the expression of ACE2 and TMPRSS2 were thought to be suitable candidates for

repurposing in the treatment of COVID-19. Oestradiol, dexamethasone, spironolactone, isotretinoin, and retinoic acid (for ACE2), as well as bicalutamide, bromhexine, camostat mesylate, and nafamostat (for TMPRSS2), are a few examples of compounds in this group. For moderate COVID-19 instances, inhibitors against dipeptidyl-peptidase 4 (DPP4), the cognate receptor for MERS-CoV, are also discovered to be a druggable target. Examples of medications undergoing clinical trials that target DPP-4 are sitagliptin and linagliptin.

In addition to examining substances that affect ACE2 and TMPRSS2, antiviral medications that target the SARS-CoV-2 S protein were investigated. FDA has permitted the use of amlanivimab, a recombinant neutralizing human lgG1κ monoclonal antibody that targets the receptor-binding domain of the SARS-CoV-2 S protein, for COVID-19 emergency use even though it has not been approved. A broad-spectrum antiviral previously used for influenza prophylaxis and treatment, umifenovir (Arbidol®, JSC Pharmastandard) has been demonstrated to inhibit S protein trimerization, while nelfinavir (VIRACEPT®, Pfizer), an antiretroviral medication for HIV, has been reported to inhibit SARS-CoV-2 membrane fusion during the replication cycle.

Drug repurposing has been discovered to benefit from compounds like chloroquine, hydroxychloroquine, artemisinin, amodiaquine, chlorpromazine, niclosamide, imatinib, artesunate, baricitinib, verapamil, and amiodarone that block SARS-CoV-2 entrance into host cells via endocytosis. Most of these medications are thought to work by raising endosomal pH and blocking endocytic proteins, which prevents SARS-CoV-2 from fusing with the membranes of the host cells [58].

7.2 Viral Replication

The following stage of the SARSCoV-2 life cycle involves the release of the viral RNA genome into the cytoplasm and the translation of the replicase genes, which combine to form the replicase transcriptase complex (RTC) after the virus has entered the host cell. Sub-genomic RNA transcription and RNA replication are carried out by the RdRP anchored in the RTC. COVID-19 repurposing candidates include antivirals that inhibit the RdRP, such as clevudine, favipiravir, galidesivir, tenofovir, and sofobuvir. Conversely, antivirals that block RNA replication, such as emtricitabine and Remdesivir, have demonstrated encouraging results in clinical trials.

The translation and proteolytic processing of viral proteins occurs after viral RNA replication. Here, danoprevir, a hepatitis C protease inhibitor, and HIV protease inhibitors such as atazanavir, saquinavir, and ritonavir were evaluated as potential repurposing options against SARS-CoV-2's 3C-like protease. Additionally, famotidine and disulfiram were suggested as potential repurposing agents against the papain-like protease of SARS-CoV-2. Furthermore, because of their antiviral qualities, autoimmune medications like interferons have been proposed as a possible COVID-19 treatment. The effectiveness of other medications, such as the tetracycline derivative doxycycline, to prevent cell fusion and viral multiplication has also been assessed [59].

7.3 Virus Assembly and Elimination

Progeny viruses are built in the endoplasmic reticulum-Golgi intermediate complex and transported in vesicles to be released by exocytosis following the synthesis and processing of the structural proteins of the virus. As potential repurposing medications, antiviral medications that target this stage of SARS-CoV-2 replication are been suggested. Oseltamivir, daclatasvir, and sirolimus for rheumatoid arthritis are a few examples of these medications. Leflunomide and brequinar have both completed clinical studies and are presently being used to treat autoimmune diseases and cancer. Because DHODH is a desirable host target, Xiong and colleagues tested the effectiveness of DHODH-targeting drugs, S312 and S416, that had previously been created by Diao and colleagues as SARS-CoV-2 antivirals. The investigation showed that although the two chemicals effectively hindered transcription, translation, and replication of the viral genome, the impairment was not severe enough to interfere with host genome-related functions. In a cell-based experiment, the compounds demonstrated exceptional antiviral efficacy and minimal toxicity, rendering them highly effective inhibitors of SARS-CoV-2. Furthermore, the compounds demonstrated strong antiviral properties against Influenza A, ZIKV, and EBOV, indicating their strong broad-spectrum antiviral activity.

That being stated, because the machinery of the host cell is the target of host-targeting drugs,

cytotoxicity problems are frequently encountered. Given that kinases are frequently essential for controlling a wide range of biological functions, toxicity is a significant concern when it comes to kinase inhibitors, such as JAK inhibitors. Furthermore, because kinases are essential to the functioning of host cells, they are frequently highly conserved. As a result, kinase-targeting medications are more likely to cause off-target side effects, which could exacerbate their cytotoxic effects. Regarding ACE2 inhibitors, toxicity is still a significant barrier to their broad usage, even if they may be effective treatments for SARS-CoV-2 infection. Many strong ACE2 inhibitors can be found using molecular docking and virtual screening. It was also noted that some of the compounds had acute theoretical toxicity because they were carcinogenic, mutagenic, or hepatotoxic, even though their docking scores were good. Moreover, it has been noted that the effects of ACE2 inhibitor chemicals differ according to the host's gender and genetic makeup; for these reasons, creating an efficient, all-arounACE2 inhibitor may prove to be a difficult task [60]**.**

8. REPURPOSING OF EXISTING DRUGS

8.1 Limitations of Drug Repurposing as a Rapid Response Strategy in COVID-19 Therapeutics

While drug repurposing promises to be a rapidly accessible strategy for the identification of treatments for COVID-19, it is not without its limitations. Several challenges have arisen in the course of the pandemic that point to the challenges involved in taking an existing approved drug into a new indication. Limitations range from pharmacokinetic considerations and issues associated with clinical trial designs to safety concerns as well as broader applicability of repurposed drugs to diverse patient populations [17].

8.1.1 Variable efficacy across populations

One of the largest drawbacks of drug repositioning is that drugs may not be universally effective for all populations. COVID-19 will always express in the heterogeneity of an individual: disease, viral load, immune response, and level of comorbidities. A promising drug in one group (e.g., mild cases or younger patients) may perform poorly in another-the elderly or the patients with several comorbid conditions. This inconsistency makes it difficult to generalize the results of clinical trials to the wider population. As an example, hydroxychloroquine appeared to have in vitro antiviral activity but showed no clinically meaningful benefit when it was given in a randomized trial and even posed risks for safety, especially to elderly or at-risk patients [68].

8.1.2 Altered pharmacokinetics in COVID-19 patients

Drug repurposing is also challenged by the alterations to PK brought about by the disease itself or by other diseases the patients may have. Severe COVID-19 cases may lead to organ dysfunction, such as liver or kidney damage, and an inflammatory environment, which will interfere with drug absorption, metabolism, and excretion. For instance, remdesivir, a drug that is hepatically metabolized, may not achieve sufficient levels for therapeutic use in the context of organ dysfunction. Additionally, drugs may be distributed poorly by ventilators or poor circulation and thus will require readjustment in the dosing schedule for optimum effect. These factors make it hard to predict the behavior of repurposed drugs against the disease in patients with COVID-19 compared to their original indications, and therefore further studies should determine the optimal dosing and safety profiles for these drugs [18].

8.1.3 Limited evidence on long-term efficacy and safety

Many repurposed drugs also have established well a safety profile associated with their original indication, although long-term efficacy when used to treat COVID-19 is largely unknown. For instance, dexamethasone has reduced lethal rates for severely-ill Covid-19, but chronic immunosuppression side effects on the management of the disease may appear to dominate, particularly when applied inappropriately to milder manifestations of the disease. Similarly, tacrolimus or the administration of any immunosuppressants creates apprehension in patients who have a propensity for secondary infections and other complications. Absent such long-term studies evaluating the full range of effects, there is a risk that repurposed drugs may expose the public to unsuspected dangers in this new context of pandemic use [69].

Table 3. Repurposing of existing drugs for COVID-19

S.NO	Pharmacological class	Drug	Proposed mechanism in the treatment of SARS-CoV-2 infection	Referenced
1.	Kinase inhibitors	Baricitinib	It could exert anti-viral effects by its affinity for AP2-associated protein AAK1, reducing SARS-CoV-2 endocytosis.	[2]
		Imatinib	It accumulates in lysosomes resulting in some antiviral activities by lysosomal alkalization required for virus/cell fusion.	
2.	Antibacterials	Doxycycline	It could reduce pro-inflammatory cytokines levels and chelate matrix metalloproteinases used for cell fusion and viral replication.	[61]
3.	Antidiabetic drugs	Dapagliflozin	During virus infection, serum lactate dehydrogenase level excessively rises. Dapagliflozin has been reported to reduce lactate levels by various mechanisms. It also reduces oxygen consumption in tissues and causes the use of glucose in the aerobic pathway.	[62]
		Linagliptin, sitagliptin	Since SARS-CoV-2 could use the DPP4 receptor to invade cells, the inhibition of DPP4 could be useful in mild COVID-19 patients.	
4.	Antimalarials	Artemisinin/artesunate	Anti-inflammatory activity, NF-κB-coronavirus effect, and chloroquine-like endocytosis inhibition mechanism	[63]
		Atovaquone Chloroquine, hydroxychloroquine	It could inhibit SARS-CoV-2 by targeting the viral RdRp or 3C-like protease They showed interference with the glycosylation of ACE-2 receptors; they increase the pH of acidic cellular organelles, counteracting virus replication.	
5.	Antitumorals	Mefloquine	It inhibited SARS-CoV-2 replication in vitro experimental models	
		Plitidepsin	It could inhibit the multiplication and propagation of SARS-CoV-2	
		Selinexor	It could inhibit the replication of SARS-CoV-2 and mediate anti-inflammatory and anti-viral effects	
6.	Antivirals	Atazanavir, danoprevir, darunavir	Potential SARS-CoV-2 protease inhibition	[64]
		Clevudin	It acts as a potent inhibitor of RdRp protein, preventing RNA replication	
		Daclatasvir	It could target different proteins of the SARS-CoV-2 life cycle, affecting both viral RNA replication and virion assembly	
		Emtricitabine	RNA synthesis nucleos(t)ide analogue inhibitors could have an effect against SARS-CoV 2 infection	
		Favipiravir, galidesivir	They inhibit RdRp of RNA viruses, blocking SARS-CoV-2 replication.	
		Lopinavir/ritonavir		

S.NO	Pharmacological class	Drug	Proposed mechanism in the treatment of SARS-CoV-2 infection	Referenced
			They could inhibit SARS-CoV-2 replication by blocking 3CLpro and PL2pro proteases.	
7.	Immunosuppressants	Cyclosporine	It can block viral replication and thus transcription of pro-inflammatory cytokines.	[65]
		Leflunomide	In vitro studies have shown antiviral effects of leflunomide against SARS-CoV-2	
		Sirolimus	It could block viral protein expression and virion release.	
		Tacrolimus	It inhibited SARS-CoV-2 replication in vitro	
8.	Interferons	Alpha and beta interferons	Interferons exhibit both direct inhibitory effects on viral replication and support an immune response to clear virus infection.	[66]
		Peginterferon lambda-1A	It inhibits viral replication and does not trigger cytokine storms. It helps the body's natural immune system into action.	
9.	Other	Amiodarone	It could reduce the internal acidity of endosomes and lysosomes affecting cell activities important for an efficient viral entry.	[67]
		Bicalutamide, bromhexine, camostat mesilate, nafamostat	Inhibition of TMPRSS2, an enzyme facilitating SARS-CoV-2 cell penetrate	
		Chlorpromazine	It inhibits clatrine-mediate endocytosis by interacting with dynamin	
		Estradiol patch	It could down-regulate ACE2 receptors in kidneys	
		Famotidine	It could bind papain-like protease, responsible for initial processing of the SARS-CoV-2 polyprotein into active subunits	
		Isotretinoin, retinoic acid	They can down-regulate ACE2 receptors; they are potential protease inhibitors; they could increase CD4 counts	
		Ivermectin	It inhibits the replication of SARS-CoV-2 *in vitro*	
		Niclosamide	It could block endocytosis of SARS-CoV-2 and prevent its autophagy by inhibiting of S-Phase kinase-associated protein 2	
		Spironolactone	It could, theoretically, reduce ACE-2 expression on lung cell surfaces.	

8.1.4 Drug-drug interactions

Most COVID-19 patients are elderly patients with multiple chronic conditions, placing them at a high risk for polypharmacy regimens. This increases the risk of drug-drug interactions (DDIs) that alter the pharmacokinetics and pharmacodynamics of both the repurposed drug and concomitant medications. For example, hydroxychloroquine will interact with drugs metabolized by the cytochrome P450 enzyme system, thereby making dangerous DDIs such as anticoagulants or antidiabetic medications a possibility. These interactions could well confound treatment approaches, particularly in seriously ill patients with multiple comorbid conditions, and extrapolations from trials which the drugs were tried which could not have foreseen these complexities are hard to make [63].

8.1.5 Inadequate preclinical information

These drugs were not designed with considerations for viral infections such as COVID-19 in mind, and mechanisms of action in the context of SARS-CoV-2 are not fully understood. For example, ivermectin was promoted early during the pandemic based on in vitro data suggesting antiviral effects against the virus but failed to confirm this result in clinical trials. Though repurposed drugs represent a promise in the lab, translating such promise to human treatment is contingent upon robust clinical evidence. These drugs did not have extensive preclinical screening for SARS-CoV-2-specific activity, especially in animal models; therefore, it would not be so easy to predict the likely success of such drugs in humans [68].

8.1.6 Regulatory and ethical issues

Drug repurposing may appear to take the quicker route to finding effective COVID-19 therapies, but regulatory hurdles still exist. Current FDA, EMA, and other regulatory agencies' procedures demand high-quality clinical data before allowing new indications for drugs under their jurisdictions, and that repurposed drugs should meet the standard of efficacy and safety. This may delay so long that one wonders whether this accelerated pace compromises the quality of safety assessments for repurposed drugs being advanced through the approval pathways. Moreover, the use of repurposed medications, where proper testing against COVID-19 may not have been made, invites ethical questions. For instance, some countries allowed medicines such as hydroxychloroquine or ivermectin for emergency use without adequate evidence that they would be effective, which may have led to negative outcomes or simply delayed finding an appropriate treatment [69].

8.1.7 Clinical trial design and data analysis heterogeneity

Issues related to trial design and data interpretation have impeded clinical trials for repurposed drugs. Considering that COVID-19 emerged rapidly, many clinical trials were conducted in an expedited manner, and designs might not control for confounding variables that would have had factors such as variations in the level of the disease, ages, comorbidities, or other viral variants. Indeed, diversified trial endpoints, various populations enrolled, and different protocols all bring in conflicting outcomes, making it hard to decide on a final verdict. For example, early remdesivir trials delivered mixed verdicts and caused more questions to be raised regarding its real-world efficacy for COVID-19 treatment. These challenges are why structurally more complex, multicentric, and adaptive trial designs are necessary when trying to encompass the tangles of COVID-19 treatment so clear, interpretable data will reveal themselves [70].

8.1.8 Narrow scope in addressing all aspects of Covid-19

Repurposed drugs may be effective for some aspects of COVID-19 treatment, like bringing down viral load or reducing inflammation but fails to cover the complete scope of disease pathology. The course of COVID-19 is multifaceted, involving both viral replication, immune dysregulation, thromboembolism, and organ damage. Many repurposed drugs have a narrow scope in targeting such complex pathology. For example, remdesivir and lopinavir-ritonavir are antiviral drugs that target the virus replication cycle, but do not address inflammation or the immune response responsible for the severe manifestations. This indicates that there is a need for combination therapy where the problems of drug interactions, side effects, and patients' compliance may arise [17,71].

9. FUTURE PROSPECTIVES

Drug repurposing, as a therapeutics rapid response strategy in COVID 19 treatment, remains a viable option with a lot of potential

especially now that there are pandemics and most likely more pandemics in the future. The development of high throughput screening and artificial intelligence (AI) technologies will mean that there will be faster searches for potential candidates that can be drugged from the already available libraries. Not only will these technologies hasten the invention process, but also enhance the accuracy of predicting the efficacies and safety levels of the drugs to be used in treating COVID-19 patients with particular indelible strains or comorbid conditions.

The design of future clinical trials protocols will not only be more flexible, but will also be based on real-world evidence and adaptive trials approaches allowing rapid testing and approval for repurposed drugs. Further, the incorporation of pharmacogenomics in drug repurposing will facilitate targeted therapy, ensuring the patients will be treated with the most effective drug for their genetic profile and severity of disease.

Drug repurposing will also extend beyond the domain of antivirals and will be used to target other disease pathology including the host immune response, inflammation and vascular abnormalities. It is possible to develop drugs designed for autoimmune disease or cancer, in the treatment of long COVID and post-viral syndrome.

10. CONCLUSION

The worldwide health crisis brought about by the COVID-19 pandemic has underscored the necessity to expedite drug discovery and swiftly pinpoint effective medications and therapeutic alternatives. Drug repurposing has emerged as a widely adopted approach aimed at minimizing research duration, as well as the associated costs and risks. While repurposed medications must still undergo clinical trials, it is clear that this strategy can quickly uncover effective drugs, including those that may have previously been unsuccessful in their initial applications. In conclusion, while drug repurposing presents a promising strategy to alleviate the limitations associated with traditional drug discovery, it continues to encounter numerous challenges from both scientific and regulatory perspectives. The emergence of new variants of SARS-CoV-2 underscores the ongoing necessity for innovative and effective treatments for COVID-19. Drug repurposing offers the potential for the swift identification of new and safe medications that can reduce the need for patient hospitalization, serving as a temporary solution until the introduction of newly developed drugs that demonstrate high efficacy against SARS-CoV-2.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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