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Life Sciences 259 (2020) 118275

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Utilizing drug repurposing against COVID-19 – Efficacy, limitations, and challenges

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ARTICLE INFO

Keywords:
Covid-19
Drug repurposing
FDA approved drugs
SARS-CoV2
Localized delivery

ABSTRACT

The recent outbreak of Coronavirus disease (COVID-19), first in Eastern Asia and then essentially across the world has been declared a pandemic by the WHO. COVID-19 is caused by a novel virus SARS-CoV2 (2019-nCoV), against which there is currently no vaccine available; and current antiviral therapies have failed, causing a very high mortality rate. Drug repurposing *i.e.* utilizing an approved drug for different indication, offers a time- and cost-efficient alternative for making new therapies available to patients. Although there are several reports presenting novel approaches to treat COVID-19, still an attentive review of previous scientific literature is essential to overcome their failure to exhibit efficacy. There is an urgent need to provide a comprehensive outlook toward utilizing drug repurposing as a tool for discovery of new therapies against COVID-19. In this article, we aim to provide a to-the-point review of current literature regarding efficacy of repurposed drugs against COVID-19 and other respiratory infections caused by coronaviruses. We have briefly discussed COVID-19 epidemiology, and then have discussed drug repurposing approaches and examples, specific to respiratory viruses. Limitations of utilization of repurposed drug molecules such as dosage regimen and associated challenges such as localized delivery in respiratory tract have also been discussed in detail.

1. Introduction

Recent outbreaks of zoonotic infectious diseases have perplexed the research community about their origin, spread and treatment. Many of the 21st century epidemic and pandemic outbreaks including SARS, MERS, Ebola, bird flu (H5N1), swine flu (H1N1), and the most recent outbreak of COVID-19 were results of zoonotic outbreaks due to animal to human transmission of infectious pathogens. A major variety of these zoonotic viruses are known to be hosted in various classes of bats, including the virus responsible for the recent outbreak of COVID-19 around the world. COVID-19 (Coronavirus Disease 2019) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), a member of Betacoronaviruses (β-CoV) genera of coronaviruses group of related viruses. In addition to Covid-19, betacoronaviruses were also responsible for 2002–2004 outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV); and 2012 outbreak of Middle East Respiratory Syndrome (MERS-dCoV), first identified in China and Saudi Arabia respectively [1–3].

The 2019 outbreak of Coronavirus Disease 2019 (COVID-19) was caused by 2019-Novel coronavirus (2010-nCoV), later officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses (ICTV) [4]. The outbreak started from Wuhan, China; and has spread all across the world, infecting approximately 14 million people with > 602,200 total deaths according to WHO's COVID-19 global case dashboard, by July 20th 2020 [5]. Like SARS-CoV and MERS-CoV, SARS-CoV-2 also belongs to the same family of Betacoronovirus. [6]. COVID-19 was declared as a Public Health Emergency of International Concern (PHEIC) by World Health Organization (WHO) on January 30, 2020; and a pandemic on March 11, 2020 [7]. Severity of this pandemic has led the world community to implement containment measures and to research collaboratively to address the knowledge gaps to identify COVID-19 therapies [8].

Many FDA-approved and investigational anti-viral drugs, alone or in combination, used in the past against SARS and MERS, are being investigated against COVID-19. However, even with massive efforts, no specific antiviral treatment or vaccination for COVID-19 is yet available [9,10]. Hence, there is an urgent need to combat this highly contagious disease, which requires a clear understanding of disease pathology and critical strategies in identifying new drugs. In addition to currently approved antiviral therapies, may alternative strategies are also being investigated including antiviral activity of natural killer cells, mesenchymal stem cells [11], immunotherapy [12] and traditional Chinese medicine [13]. Although several new therapeutic strategies are

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https://doi.org/10.1016/j.lfs.2020.118275
Received 21 July 2020; Received in revised form 10 August 2020; Accepted 10 August 2020
Available online 17 August 2020
0024-3205/

emerging in these desperate times, further clinical trials are needed to ensure safety and efficacy of the new drugs [6]. As traditional drug development process is tedious and expensive, repurposing of known drug molecules against COVID-19 has become an elegant strategy to quickly develop effective therapies, evident from wide-spread information about efficacy of antimalarial drugs, chloroquine and hydroxychloroquine [14–17].

Although promising, most of the current studies present preliminary and contradictory findings; and current research requires to be strengthened with strong and significant clinical evidence gathered through extensive studies with significant number of patients while circumventing misconceptions, so as to mitigate any possible risks associated with new treatment regimens [18,19]. Moreover, even after identifying repurposed drugs, there are several challenges to overcome in terms of dose adjustments; acute/chronic toxicity; and choice of appropriate delivery system and route of administration to deliver repurposed drugs. Thus, despite identification of numerous repurposed drugs, there is an urgent need to review the repurposing strategies, limitations of repurposed drugs and respective delivery approaches to deliver them precisely for implementing an instrumental battle against COVID-19.

2. Drug repurposing as an approach for drug discovery

Drug repurposing approach puts the drug discovery process in fast track, and has been gaining attention from the researchers in wide range of scientific fields [20,21]. Due to the availability of *in-vitro* and *in-vivo* screening data, complete chemical optimization, toxicity studies, bulk manufacturing, formulation development and pharmacokinetic profiles of FDA-approved drugs, drug development cycles are shortened as all these critical steps can be bypassed [22,23]. In addition, there is no need of larger investments and repurposed drugs are proven to be safe in preclinical models thus lowering the attrition rates as well [20,24]. Hence, the main advantages of drug repurposing are associated with established safety of the known candidate compounds, substantially reduced development time frames and costs associated with advancing a candidate into clinical trials [22].

In the past, most of the repurposed drugs were discovered serendipitously. Apart from serendipitous observations, drug repurposing can be executed through several strategies including binding assays and phenotypic screening methods or computational methods, as presented in Table 1 [23]. Recent developments have opened the doors to use drug repurposing approaches that do not rely on generating empirical data related to binding characteristics or mechanism of action. Exhaustive review on drug repurposing approaches and their practical application have been reported by Pushpakom et al. [21], Talevi [25], Parvathaneni et al. [23] and Xue et al. [26].

In a nutshell, phenotypic approaches involve *in-vitro* and *in-vivo* based screenings while the challenges include hit validation and target deconvolution [23]. On the other hand, network-based approaches discover novel drug-disease relationships or drug-target relationships with high prediction accuracy with limitations including inability to detect overlapping clusters [26]. Drug-centric approach connects a known drug to a new target and predicts associated new indication. Available structure-based techniques for drug-centric repositioning include molecular docking to screen single compounds against a library of protein structures, pharmacophore modelling algorithm to screen protein–ligand 3D pharmacophoric features describing the ligand's binding and protein–ligand interaction profile similarity approaches. Target-based approach links a known target and its established drug to a new indication. However, it requires a deep understanding of the molecular relationship between the target and the disease [29]. Knowledge-based approaches consolidate known information about a drug to anticipate previously unexplored mechanisms including presence of unidentified drug targets for old drugs, undiscovered drug–drug similarities and new biomarkers [23]. Selection of suitable approach is a crucial step in drug repurposing. The opportunities for drug repurposing are diverse, but a lot still has to be done for its exploration. Time frames involved in the current research toward treatment and prevention of SARS-CoV-2 infection/COVID-19 are represented in Fig. 1 [43].

Lately, several researchers have reported the anti-COVID efficacy of known repurposed drugs through some *in-vitro*, preclinical and clinical trials [18,31]. For instance, chloroquine, an anti-malarial drug was reported to be effective against SARS-CoV in earlier studies, and is also being considered a top candidate among anti-COVID-19 therapeutics [32,33]. In another study, Caly et al. investigated and reported ivermectin, an FDA-approved anti-parasitic, for its anti-viral activity *in-vitro* [34]. Other studies have highlighted the potential of Angiotensin Receptor Blockers (ARBs) [35], interferon-alpha (INFα) [11], lopinavir/ritonavir [36], arbidol [37] and niclosamide [38] as considerable treatment options against COVID-19. Apart from all these studies, drugs such as remdesivir, teicoplanin, favipinavir *etc.*, which showed promise against SARS-CoV, MERS and influenza [39], are also being studied for their efficacy and safety in COVID-19 [38,40]. Other drugs alone or in combinations which are under investigation include oseltamivir, hydroxychloroquine, azithromycin [41]. Eli Lilly and Company has initiated phase III clinical trials to evaluate baricitinib's potential as COVID-19 treatment [42], whereas, baricitinib (anti-rheumatoid) has been identified for its repurposing potential against COVID-19 using artificial intelligence algorithms by Stebbing et al. [43]. Rosa et al. has reported few ongoing clinical trials emphasizing the importance of drug repurposing for COVID-19 treatment [19].

3. Utility and examples of repurposed drugs for respiratory viruses including SARS-CoV-2

Respiratory viral infections are generally caused by six of the major groups of respiratory viruses: rhinoviruses, coronaviruses, respiratory syncytial viruses, metapneumoviruses, parainfluenza viruses, and adenoviruses. Occasionally, herpesviruses also cause pharyngitis and lower respiratory tract disease in immunosuppressed patients [44]. Out of those respiratory infections, outbreaks of lower respiratory tract disease

Table 1
Brief overview on different drug repurposing approaches.

Repurposing approach	Description	References
Binding assay	Identify binding interactions of ligands to assay components	[21]
Phenotypic Screening	Evaluates a large number of authorized or evolving drugs in various prognostic models Evaluation of a series of compounds in an array of independent models	[21,27]
Pathway based or Network mapping	Involves constructing drug or disease networks based on gene expression patterns, disease pathology and protein interactions	[28]
Drug Centric	Uses structural information of the target site Examine effects of a single drug on multiple targets	[29]
Target based	Identification of new indication based on drug's protein targets	[28]
Knowledge-based	Consolidates known information about a drug anticipating unexplored biomarkers	[23]
Signature based	Based on the comparison of the unique characteristics or 'signature' of a drug against that of another drug, disease or clinical phenotype	[21]

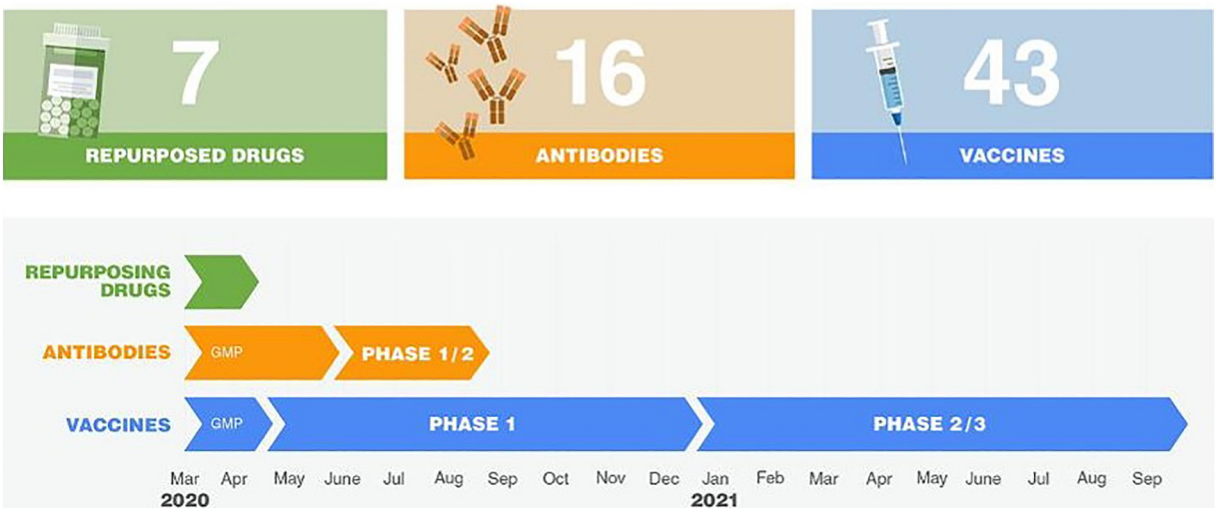

Fig. 1. Representation of timeline for SARS-CoV-2 Infection (COVID-19) treatment and prevention [30].

associated with coronaviruses (SARS-CoV and MERS-CoV) and influenza are unforgettable [22]. Till date, no effective vaccines or drugs are approved to treat SARS and MERS, although many are in (pre)clinical development. Development of effective therapeutics is associated with consideration of underlying molecular mechanisms in virus replication and pathogenesis; and virus–host communications, representing its complexity.

Transmembrane spike (S) glycoprotein on SARS-CoV2 enables entry of coronavirus into host cells through formed homotrimers protruding from the viral surface [45]. Gordon et al. identified 332 high-confidence protein interactions between SARS-CoV-2 proteins and human proteins using affinity-purification–mass spectrometry (AP-MS) analysis; and identified angiotensin-converting enzyme 2 (ACE2), expressed in type 2 alveolar cells in the lungs, has been identified as a major SARS-CoV-2 receptor. Authors also studied the interacting human proteins for their biological functions, anatomical expression patterns, and expression changes during SARS-CoV-2 infection. Major cell processes of interacting proteins, including lipoprotein metabolism, nuclear transport and ribonucleoprotein complex biogenesis have been identified by the authors [46]. S glycoprotein of coronavirus is surface-exposed and moderates virus entry into host cells. Thus, it is the main target of neutralizing antibodies which direct therapeutic and vaccine design [45].

Interestingly, hydroxychloroquine (HCQ) interacts with virus through ACE-2 glycosylation [47]. Transcription and translational properties to the viral RNA are attained by Transcriptional regulatory elements present in 5′ and 3′ untranslated regions. Thus, understanding the genetic annotation, the sequences in the sub-genomic mRNAs, and more insight into the secondary structures of the genomic RNA would enable development of genome targeted therapeutics [48]. The main protease (M^{pro}) is necessary for virus proteome production and replication. Therefore, M^{pro} is considered as one of the potential targets to treat COVID-19.

In addition, RNA polymerase unit is another promising target to develop viral inhibitors. Remdesivir inhibiting the RNA dependent RNA polymerase (RdRp) protein is currently under clinical investigation for the treatment of COVID-19 [48]. Chen et al. performed virtual screenings using SARS-CoV-2 3C-like protease and reported the inhibitory activity of velpatasvir/sofosbuvir and ledipasvir/sofosbuvir on viral enzymes [49]. To combat old, emergent viruses especially in the current public-health emergency, it is imperative to identify therapeutics in treating coronavirus infection. In this context, exploring the repurposing ability of known drugs can represent an effective strategy for identification of new antiviral agents while identifying new pathways and targets involved [50].

Drugs investigated for the treatment of SARS/MERS may inhibit the replication of coronaviruses, and may be useful in an attempt to discover therapeutics in COVID-19 treatment [50]. Earlier drug repurposing studies targeting SARS and MERS caused by different strains of coronaviruses could also be supportive in exploring treatment options for COVID-19 [51,52]. Different drug repurposing scenarios in antiviral drug discovery are presented in Fig. 2. Efforts have been made to report the successfully repurposed drugs and current position of drugs under investigation, presented in Table 2. Here, different strategies of drug repurposing are being applied to identify efficacy of known drugs in respiratory viral infectious diseases utilizing both bioactive small-molecule collections screening and computational methods.

3.1. Drug repurposing scenarios in antiviral drug discovery

3.1.1. Same target – new virus

If an antiviral drug has the ability to target a specific pathway exploited in replication of viruses and is active against other viruses, it may have the potential to be useful against COVID-19 [50]. Remdesivir, an investigational broad-spectrum antiviral drug has exhibited promising efficacy in MERS and SARS treatment. Several recent studies have reported the effectiveness of remdesivir in COVID-19 treatment [53]. Similarly, chloroquine (approved for the treatment of malaria) has exhibited repurposing potential against influenza [54], MERS (inhibit replication of virus) [55], SARS [56] and COVID-19 [53,57]. Also, hydroxychloroquine (HCQ) has demonstrated beneficial impact in treating COVID-19 reported in several recent studies [57,58]. On March 28th 2020, the Food and Drug Administration (FDA) granted emergency use authorization (EUA) for the use of chloroquine phosphate and hydroxychloroquine sulfate to treat COVID-19 [59]. Also, FDA has issued Emergency Use Authorization (EUA) for remdesivir in treating COVID-19 on May 1st, 2020 [60]. However, on June 15, 2020, FDA revoked EUA for emergency use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate based on ongoing analysis of the EUA and the emerging scientific data [61].

3.1.2. Same target – new indications

This type of scenario can be applied if a known drug has the ability to modulate pharmacological target (*i.e.*, a protein or a pathway), essential in a pathogenic process associated with a viral infection [50]. For example, imatinib (anti-cancer drug) inhibits cellular Abelson (ABL) kinase and was found to be active against pathogenic coronaviruses [52].

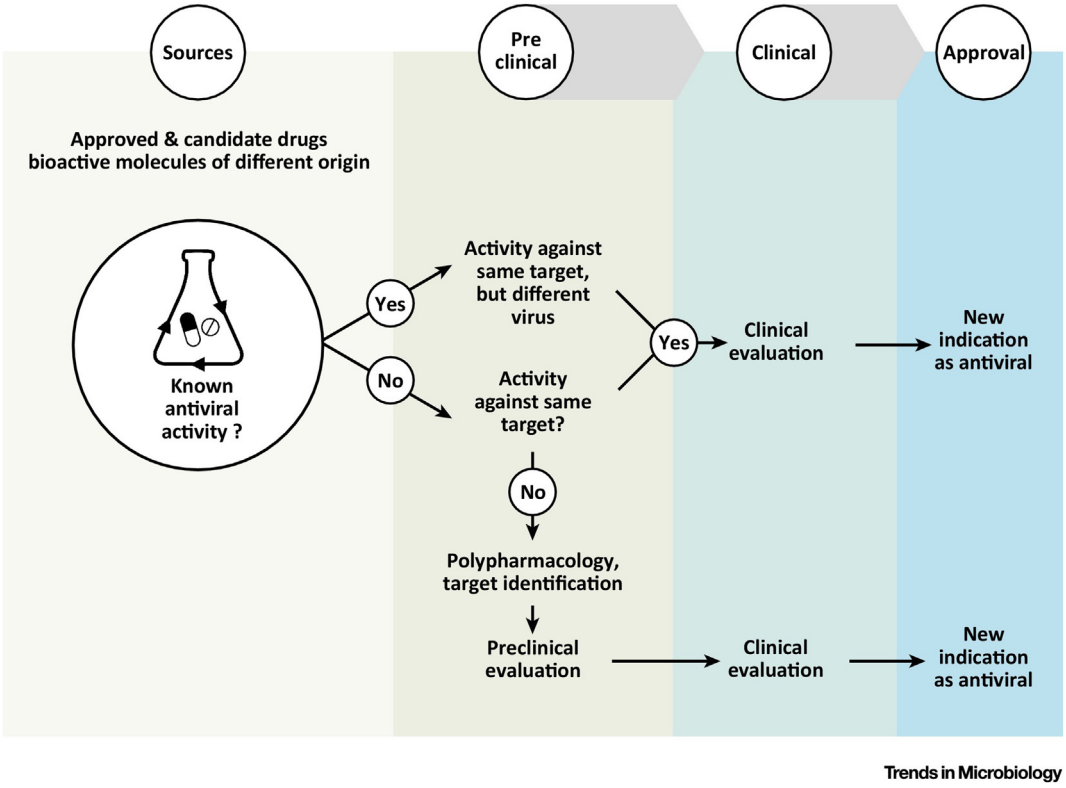

Fig. 2. Possible scenarios of drug repurposing in antiviral drug discovery [50].

3.1.3. New target – new indications

This kind of scenario occurs, when an approved drug with an established bioactivity in a specific pathway is identified with a new molecular target, essential for virus replication. Antimicrobial agents such as teicoplanin, itraconazole, and nitazoxanide were found to have ability to inhibit virus-infected cells, further inhibiting viral replication [65,66].

3.2. Recent case studies emphasizing drug repurposing in COVID-19 treatment

Zhou et al. utilized powerful network-based methodologies to identify drugs and potential drug combinations with repurposing potential targeting SARS-CoV-2 [67]. Combinations of Sirolimus, dactinomycin; mercaptopurine, melatonin and toremifene plus emodin were identified as potential treatment options [67]. Shah et al. carried out *in-silico* studies to identify docking interactions with COVID-19 enzymes using library of known 61 antiviral drugs (used in clinics/under investigation) [68]. HIV protease inhibitors and RNA dependent RNA polymerase inhibitors have also been reported to exhibit close interaction with this enzyme. Usefulness of methisazone, CGP42112A and ABT450 has been reported for their efficacy as a convenient treatment for COVID-19 due to their ability to act as protein synthesis inhibitor, angiotensin AT2 receptor agonist and an inhibitor of non-structural

Table 2
Repurposed drugs in clinical development against different indications caused by respiratory viruses.

Drug/compound	Original indication	New use in respiratory virus infections	Status	References/clinical trial details
Sarilumab	Rheumatoid arthritis	COVID-19	Phase 2	NCT04315298
Favipiravir	Influenza	COVID-19	Phase 3	NCT04336904
Remdesivir	Broad spectrum Anti-viral	COVID-19	Completed phase 3	[62]
Danoprevir/ritonavir	Danoprevir for Hepatitis C Ritonavir for HIV	COVID-19	Completed phase 4	NCT04345276
Dexamethasone	Immunosuppressant	COVID-19 associated Acute Respiratory Distress Syndrome	phase 3	NCT04327401
Ivermectin/doxycycline	Ivermectin for Parasitic infections Doxycycline for bacterial infections	COVID-19	Phase 2	NCT04407130
ASC09/ritonavir	Ritonavir for HIV	COVID-19	Phase 3	NCT04261270
Hydroxy-chloroquine	Malaria	COVID-19	Phase 2	NCT04333225
Methylprednisolone	Immunosuppressant	COVID-19	Phase 4	NCT04263402
Tocilizumab	Cytokine release syndrome	COVID-19	Phase 2	NCT04317092
Tocilizumab	Cytokine release syndrome	SARS-CoV-2 infection with severe pneumonitis	Phase 2	NCT04315480
Diltiazem	Anti-hypertensive	Influenza A	Phase 2	NCT03212716
Nitazoxanide	Antiprotozoal agent	Influenza	Completed phase 2 & 3	[63]
Interferon B1b	Relapsing-remitting and secondary-progressive forms of multiple sclerosis	MERS	Completed phase 2 & 3	[64]

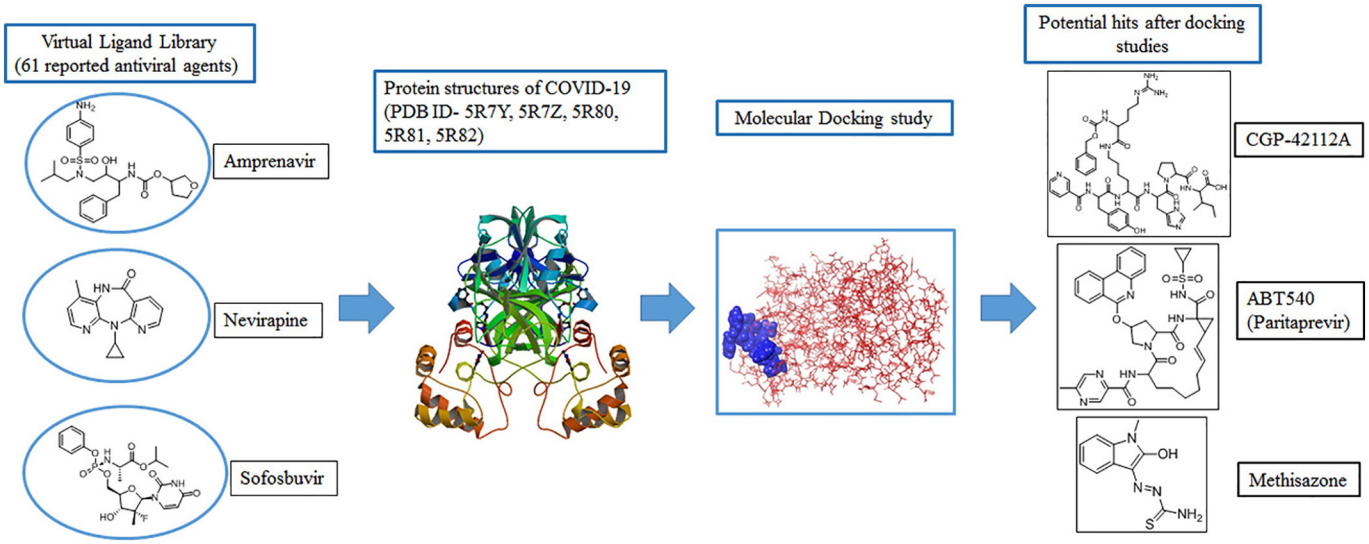

Fig. 3. Overview on *in silico* molecular docking study conducted for screen library of antiviral drugs to identify potential hits in COVID-19 treatment [68].

protein 3-4A respectively. An overview of this study is presented by the authors in Fig. 3.

In another study, Zhang et al. assumed excessive inflammation, depressed immune system and activated cytokine storm as noticeable contributors/markers in COVID-19 pathogenesis [69]. Melatonin, known for its anti-inflammatory, anti-oxidative, and immune enhancing activities has attained great attention in the search for COVID-19 treatment. Zhang et al. evaluated the adjuvant effects of melatonin in diminution of the cytokine storm by targeting several key steps in the process. Possible beneficial effects of melatonin as adjuvant use in COVID-19 have been demonstrated in respiratory disease models induced by infections and associated complications [69].

Structural proteins (Spike, Nucleocapsid, Matrix (M) and Envelope) and non-structural proteins such as RNA dependent RNA polymerase (RdRp) were reported as characteristic proteins of human coronaviruses [70]. RdRp was found to be a crucial enzyme in the life cycle of SARS-CoV-2 [71]. Based on this information, Elfiky et al. evaluated anti-polymerase drugs such as sofosbuvir, ribavirin, remdesivir (FDA approved antiviral drugs) and IDX-184 (under clinical trials to testing against different viruses) against COVID-19 through *in-silico* testing. Authors developed a model for COVID-19 RdRp using homology modelling after sequence comparison to the available structures in the protein data bank (PDB). Later, molecular docking (aid of AutoDock Vina software implemented in SCIGRESS) was performed to test few direct-acting antiviral (DAA) drugs such as sofosbuvir, ribavirin, remdesivir, IDX-184) *etc.* Moreover, native nucleotides GTP and UTP were also tested against COVID-19 RdRp model [72]. It was reported that coronavirus polyprotein encoded a main protease called 3-C-like protease (M-pro; PDB ID 6lu7) [73]. Later, first virtual screening of FDA approved drugs dataset (Selleckchem Inc. (WA, USA)) using Schrodinger glide docking module against COVID-19 was also performed [1]. From docking results, ribavirin (original indication: respiratory syncytial virus infection), telbivudine (original indication: anti-hepatitis B virus infection), vitamin B12 (vitamin) and nicotinamide (original indication: tuberculosis) were identified as the most feasible candidates with repurposing potential against COVID-19. Authors also identified the high similarity of SARS and COVID-19 M-pros, thus enabling utilization of SARS therapies such as ribavirin in COVID-19 treatment [1]. Similarly, $3CL^{PRO}$ main protease has been targeted by Hall et al. in a study where they identified zanamivir, indinavir, saquinavir, and remdesivir as potential inhibitors of that protease through screening several antivirals utilizing homology modelling and *in-silico* molecular docking [68]. Even, Flavin Adenine Dinucleotide (FAD), adeflavin and Coenzyme A were reported for their potentiality in treating SARS-CoV-2 infection [74].

Due to the importance of S protein of SARS-CoV-2 in viral replication, several researchers have explored many known drugs like chloroquine (CLQ) and hydroxychloroquine (HCQ) [75]. Even though, FDA earlier announced EUA for HCQ usage in COVID-19, it has since been revoked due to ineffectiveness and severe cardiac adverse effects [61]. Angiotensin-converting enzyme-2 (ACE-2) receptor is known to be crucial in the entry of S-protein in cells. In addition, sialic acids linked to host cell surface gangliosides are also vital in viral replication [75,76]. *In-silico* studies have revealed that CLQ and HCQ bind to ganglioside GM1 [77]. *In-silico* analyses were performed by Fantini et al. using Hyperchem and Molegro Molecular viewer. CLQ and HCQ displayed molecular groups which bind to gangliosides similar to S protein. From the overall simulation results, HCQ was found to be more potent than CLQ against SARS-CoV-2 due to its increased fit because of stabilized contacts through CLQ-OH/CLQ-OH interactions (Fig. 4).

Overall, strategies such as computational tools and molecular docking help to reduce the resource requirements and expenses for researchers involved directly with the experimental and clinical studies, with a higher probability of obtaining the desired responses and fewer trials as reported by Panda et al. [78]. In this study, authors performed structure-based drug design (Screen ChEMBL antiviral compounds) and further carried out molecular docking analysis of screened drugs against target proteins [78]. In addition, intrinsic atomic interaction and binding conformation of the hit drugs were also validated by atom-

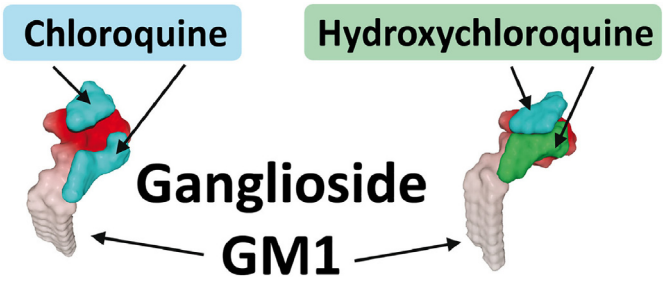

Fig. 4. Left side, surface view of GM1 complexed with two CLQ molecules represented in blue color, demonstrating the geometric complementarity of GM1 and CLQ molecules. Right side, one GM1 molecule accommodating two distinct CLQ-OH molecules represented in blue and green colors [75]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

based atom simulation. Similarly, while utilizing various advanced tools, hit drugs can be further proceeded with consequent studies, thus reducing the translational distance between preclinical test results and clinical outcomes which eventually helps to address a major challenge for the rapid development of practical treatment approaches for the ongoing COVID-19 pandemic [78].

4. Limitations of identified repurposed molecules

Despite enormous efforts and research in the field of drug repurposing, major hindrances still exist in further utilization of repurposed drugs, including issues related to therapeutic dosage, safety and delivery capabilities. The main concern associated with repurposed drugs involves establishing a dosage within the approved therapeutic margin, demonstrating therapeutic activities during clinical studies. It has rarely been reported to discover new drug-target interactions within approved therapeutic window. Higher dose required for efficacy against new indications and necessity to reconsider the route of administration significantly affects further progress of repurposed drugs. If the dose requirement to exert potency falls outside that range, it is required to conduct safety studies. Thus, achieving clear therapeutic benefits, clinical utility of finding novel drug-target interactions of repurposed drugs within well-defined safety margins is sometimes not feasible [79]. Specifically, most of the times effective concentrations required for antiviral activity are often higher than those clinically achievable with the approved regimens. Even though a smaller number of clinical studies are required for repurposed drugs, it is mandatory to conduct clinical trials with respect to efficacy (against new indication). Hence, the major distinction between *de-novo* drug discovery and repurposing is lost while diminishing the benefits of drug repurposing. In some cases, repurposed drugs are supposed to be delivered through different administration routes to exert intended activity against new indication. In certain cases, stability of the repurposed drug is also another issue to be tackled through protecting it using suitable carrier systems [13,80,81].

Physicochemical properties such as solubility, permeability *etc.* of repurposed drugs may pose a problem for their utilization. Release profiles of repurposed drugs' dosage forms are required to be modulated to establish effective therapeutic activity. Other crucial factors which need to be considered for a repurposed drug are suitable pharmacokinetic and biodistribution parameters [81,82]. Certain properties such as efficient intestinal permeability, sustained/controlled release profile, ability to cross blood-brain barrier and cellular penetration are needed to be possessed by repurposed drugs as per the respective desired applications [81]. Accordingly, drug repurposing may require additional efforts to make use of identified candidates against new indication [81]. In addition, till date, no stringent regulations or guidelines have been released by any regulatory agencies including the FDA related to drug repurposing. Thus, it is a difficult task for upcoming start-ups to provide applicable information to regulatory bodies, which poses a potential hurdle in drug repurposing [23].

5. Preventive and therapeutic agents explored against COVID-19

Several researchers across the world are putting their efforts to find an effective strategy to prevent and/or treat the current pandemic, COVID-19. However, there is no approved treatment till today. Still, the search for potential treatment for prophylactic and therapeutic applications against COVID-19 is continuing vigorously. Majority of the current investigations are attempting to turn existing drugs to prevent or treat the disease. In absence of specific antiviral treatment, strategies for COVID-19 prevention should be emphasized with great attention. As repurposed drugs are immediately available with complete safety profile, they may constitute a first line of defense against new viral infections. There are several drugs which are shown to serve as a prophylactic measure to prevent spread of COVID-19 infection. Czuppon et al. used a stochastic model to describe the early phase of a viral infection and reported that drugs blocking viral entry into target cells are more effective than drugs reducing viral production or enhancing infected cell death [83]. Drugs that could be successfully be used in a prophylactic regime have also been reported by Shetty et al. [84]. In this study, authors categorized potential prophylactic agents into two groups. First group consisted of drugs capable of inhibiting the viral entry and genome release processes required for a successful infection. These included viral uptake receptor antibodies (Angiotensin Converting Enzyme 2 (ACE2) blockers, Angiotensin Receptor Blockers (ARBs)), competitive blockers of viral uptake, inhibitors of endocytosis and viral genome release (such as chloroquine) and replication (such as Ribavirin) *etc.* [84]. The second group of prophylactic agents included factors that enhance the anti-viral host immune response [84].

Chloroquine (CQ) is known to inhibit terminal glycosylation of ACE2, the receptor that SARS-CoV-2 targets for cell entry. When ACE2 is in its unglycosylated state, it may less efficiently interact with the SARS-CoV-2 S protein, further inhibiting viral entry [85]. A current clinical trial (COVIDAXIS trial) is evaluating the chemoprophylaxis of COVID-19 infection in health care workers by hydroxychloroquine (HCQ) or lopinavir/ritonavir *versus* placebo [86]. Several trials exploring use of CQ or HCQ for prophylaxis of COVID-19 are underway. Despite lack of data on prophylaxis, the Indian Council of Medical Research (ICMR) has already recommended HCQ as pre-exposure prophylaxis for frontline healthcare workers having “high-risk” contact with patients with suspected or confirmed COVID-19, and post-exposure prophylaxis for healthcare workers (ICMR 2020) [85]. In addition to ACE receptor, presence of transmembrane protease serine2 (TMPRSS 2) is also required for spike protein priming. Researchers found that Camostat mesylate, a serine protease inhibitor, could block the entry of SARS-CoV-2 virus into lung cells, and thus might be effective against COVID-19. However, the application of Camostat for COVID-19 prevention or treatment still requires clinical trials [87]. Other investigations include evaluating Angiotensin (ARBs) and recombinant human Angiotensin Converting Enzyme 2 (ACE2) in both the treatment and prevention of SARS-CoV-2 infection [76]. In addition, a drug that would consistently prevent progression of COVID-19 would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection, and would offer a reliable therapeutic tool in COVID-19 prevention [88].

Clinical trials are underway to test the efficacy of several antiviral drugs such as favipiravir [89], remdesivir [62], danoprevir/ritonavir [90] including lopinavir/ritonavir [36], and (hydroxy)chloroquine [83]. Other studies have highlighted the repurposing potential of Angiotensin Receptor Blockers (ARBs) [35], arbidol [37] and niclosamide [38] as considerable treatment options against COVID-19. Apart from all these studies, teicoplanin which showed promise against SARS-CoV and MERS is also being studied for its efficacy and safety in COVID-19 to explore therapeutic treatment options [38,40].

6. Challenges associated with delivery of repurposed drugs

Following successful repurposing, benefits of repurposed drug could only be achieved through utilization of suitable drug delivery systems and optimal route of delivery. Hence, success in drug repurposing is compounded by the fact that not only several basic and clinical disciplines have to congregate, but formulation and delivery route aspects are also to be considered. In certain cases, repurposed drugs may be required to be delivered through delivery systems and routes of administration, different from approved dosage regimen, thus demanding their reformulation. Thus, reformulation or necessity to couple the formulation with right drug delivery device are challenges that may need to be confronted when developing suitable formulations. This necessitates the integration of pharmaceutical sciences with toxicology to achieve dose reductions (safer doses) by accomplishing targeted/localized drug delivery [91]. Especially, to combat infections caused by

respiratory viruses, it is crucial to localize the therapies efficiently to particular targets at disease's focal region in the lungs. Hence, appropriate delivery devices or formulations could be applied to provide drug exposure to the targeted tissue, while limiting exposure to other tissues [80]. Finding novel formulations or delivery mechanisms is of utmost importance in achieving localized drug delivery in the respiratory tract. Even for repurposed drugs; safety, efficacy, quality, and usability must be established, either from previous knowledge or through newly produced data [91].

Pulmonary drug delivery route to treat these respiratory virus infections has been recognized as an advantageous approach [80]. Merits of pulmonary delivery of repurposed drugs include the ability of drug aerosol to be directly targeted to its intended site of action in the lungs, thus enhancing available drug concentrations in the lungs [92]. This approach also minimizes drug accumulation elsewhere in the body, resulting in lower incidences of side-effects. Moreover, hepatic first-pass metabolism which causes inactivation of drugs can be avoided [80]. In this context, to utilize full potential of hydroxychloroquine in combating COVID-19 and to overcome the challenges encountered during its oral delivery, Pulmoquine Therapeutics Inc. have initiated investigation of aerosolized hydroxychloroquine benefits, thus resolving the issues such as slow onset of action while minimizing side-effects by providing local delivery [93].

Williams et al. recently described repurposing potential of niclosamide (an FDA approved anthelminthic drug) against SARS-CoV-2 infection and recently confirmed its antiviral efficacy [94]. Due to poor absorption, oral administration of niclosamide is a limiting factor in its ability to reach the infection site. Hence, these researchers are now considering new drug delivery formulation technologies to increase niclosamide's absorption into the body, designing the drug so that it can be inhaled directly into the lungs to be effective at treating and preventing serious SARS-CoV-2 infection symptoms. Since SARS-CoV-2 has shown to be particularly detrimental to the lungs, delivering therapeutics directly to the site may prove an effective prevention/prophylactic strategy, and provide additional treatment options [94].

7. Expert opinion and conclusions

Due to expensive and time-consuming traditional drug discovery process with higher failure rates, drug repurposing is becoming a promising tool in drug discovery. Drug repurposing facilitates identification of new uses of old drugs in shorter timeframes, while being cost-effective with reduced attrition rates, thus ultimately benefitting patients and the healthcare system overall. With increasing number of emerging viral infections day by day, discovery of therapeutics is required to be in tandem. Even though several therapeutics have shown to be effective against various respiratory viral infections such as influenza and certain strains of coronaviruses, emergence of resistance to existing antiviral drugs is becoming the major challenge. Moreover, new strains of viruses like SARS-CoV-2 are emerging creating a pandemic situation. Repurposing FDA-approved drugs is a highly efficient way to leverage drugs with known safety profiles to fight the coronavirus outbreak. However, proper delivery system and route of delivery has to be selected for dose reduction and to deliver repurposed drugs locally to the target site. With therapeutic delivery intervention, repurposing could be a perfect opportunity. Moreover, an integration of pharmaceutical sciences and toxicology is essential to tackle issues related to dosing and safety. Thus, to treat infections caused by several viruses such as SARS-CoV-2, a quick focus on collaborative research on drug repurposing along with an optimal drug delivery strategies and inhaler devices is essential.

Funding

This project was funded with the start-up funds to Vivek Gupta by College of Pharmacy and Health Sciences, St. John's University, Queens, NY. Vineela Parvathaneni was supported with a doctoral fellowship from College of Pharmacy and Health Sciences, St. John's University.

Declaration of competing interest

The authors declare that there is no competing interest in this work.

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