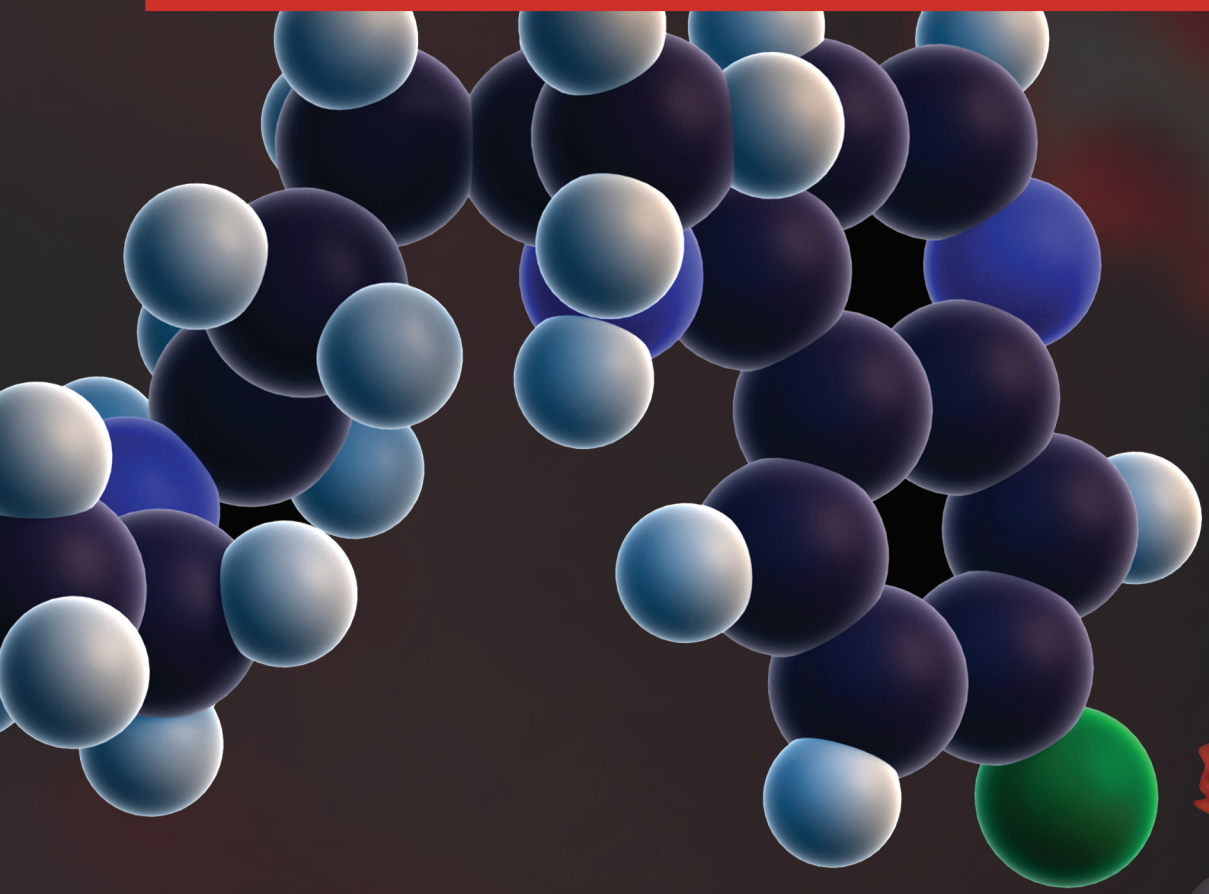
DRUG REPURPOSING AGAINST SARS-CoV-2



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Drug Repurposing Against SARS-CoV-2

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FOREWORD

Drug repurposing is a process of identifying new uses of approved or investigated drugs. In the current scenario of deadly contagious coronavirus disease 2019 (COVID-19), where no specific treatment options are available, drug repurposing is considered a very effective drug discovery strategy and could be considered the new avenue for the treatment of COVID-19. The book entitled **"Drug Repurposing against SARS-CoV2"** offers comprehensive and systematic coverage of repurposed and adjuvant drugs highlighting their therapeutic status in COVID-19 patients while assessing the challenges and ethical issues related to repurposing drugs.

The pathophysiology of SARS-CoV2 replication in COVID-19 and their modulation by repurposing drugs is explained in simple and lucid language and also through enriched illustrations. The wealth of information assembled by the authors will be useful to both Pharmacologists and Clinicians.

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PREFACE

There are seven chapters in this book entitled " Drug Repurposing against SARS-CoV2." The book focuses on current trends in drug repurposing against SARS-CoV2.

The goal of this book is to give readers an overview of drug repurposing in life-threating diseases, drug repurposing in COVID-19, as well as various techniques involved in drug repurposing. The book aims to target students, research scholars, and physicians interested in the topic. The book's structure is well-organized and updated.

Chapter 1 by Ruchi Chawla discusses repurposing drugs: a new paradigm and hopes for life-threatening diseases.

Anand *et al*., in Chapter 2, outline the repurposed and adjuvant drugs in COVID-19 patients, as well as challenges and ethical issues related to drug repurposing. Chapter 3 by Neelam *et al*. presents the repurposed drugs against SARS-CoV-2 replication in COVID-19. In Chapter 4, Awesh Yadav *et al*., describe the targeting of viral entry pathways through repurposed drugs in SARS-CoV-2 infection.

Repurposed drugs or potential pharmacological agents targeting cytokine release, and induction of coagulation in COVID-19 are discussed in Chapter 5 by Arpita Singh *et al*. In Chapter 6, Qidwai *et al*., discuss the High-throughput screening (HTS) method for screening of known drugs. The last chapter by Khan *et al*., discusses drug repurposing for COVID-19 using computational methods.

I believe this book will be of tremendous interest to students, doctors, researchers, and even patients and their families. Finally, I would like to express my gratitude to all of the contributors to this book, as well as the Bentham Publishing Editorial Board for providing us with this invaluable opportunity.

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CHAPTER 1

Repurposing Drugs: A New Paradigm and Hopes for Life-threatening Diseases

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Abstract: The process of repurposing drugs is an alternative to the conventional drug discovery process. It is a cost-effective and time-efficient process with high returns and low risk that utilizes mechanistic information of the existing drugs to investigate their novel applications against other disease conditions. The most significant benefit of drug repositioning is that it brings new life against novel/ orphan/ resistant diseases and pandemic outbreaks like COVID-19. As a result, widespread use of the drug repurposing strategy will not only aid in the more efficient fight against pandemics but will also combat life-threatening diseases. Therefore, repurposing drugs can provide a quick response to these unpredictable situations. In this chapter, we have tried to focus on various drug-repurposing strategies along with therapeutics for repurposing drugs against life-threatening diseases wherein little or no treatment is readily available.

Keywords: Drug-repurposing, Life-threatening diseases, New drug development, Phenotype screening.

INTRODUCTION

Drug repositioning is an alternative approach in drug development that opens new avenues for diseases wherein there is lack of appropriate treatment approaches. Drug repositioning (also known as drug repurposing, drug reprofiling, or drug re-tasking) is the process of identifying new modes of action, new indications, as well as new targets for already approved drugs or investigational drugs which have not been mentioned in any of the existing medical indications [1]. The availability of pre-clinical and clinical data allows for effective repurposing and the possibility of failure is relatively low in comparison to that of a new drug. As a result, the repurposed medicinal products require less time for clinical trials and regulatory approval [2]. The process of repurposing provides an abridged route to

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the conventional drug discovery process. It is a cost-effective and time-efficient process with high returns and low risk that utilizes mechanistic information of the existing drugs to investigate their novel application against other diseases and pathological conditions [3]. The most significant benefit of drug repositioning is that it brings new life against novel, orphan, resistant diseases and pandemic outbreaks like COVID-19. As a result, widespread use of the drug repurposing strategy will not only aid in the more efficient fight against pandemics but will also combat life-threatening diseases [4].

Life-threatening diseases are chronic, mainly debilitating diseases that significantly reduce a person's life expectancy. Major life-threatening diseases include cancer, diabetes, neurological conditions, coronary cardiovascular conditions and HIV/Aids [5], which are significantly impacting the global health economy. These life-threatening diseases can be prevented and treated, however, at times there is lack of response from the existing therapy. There might be a need for an alternative therapeutic regimen wherein, repurposing drugs can provide a potential backup for the same [4]. Sometimes, there are unexpected pandemics when life-threatening conditions emerge and no treatment is available, and under such circumstances, repurposition of drug products could be helpful. The majority of drugs currently repositioned in the market are a result of serendipity. The well-known cardiovascular benefits of aspirin are among one of the most appropriately proven examples of repurposing. The results of clinical trial shifted the use of sildenafil from coronary artery disease to erectile dysfunction. Bupropion was initially developed as an antidepressant before its application in cessation of smoking. Botox (on botulinum toxin A) which was first used to treat eye muscle disorders, is currently having a widespread application in cosmetic and beauty industry. Minoxidil was used to treat high blood pressure prior to the discovery of its effect on hair growth. Thalidomide and its extracts have been repurposed to treat leprosy, multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma, and metastatic prostate cancer [6, 7].

New drug development is a challenging process requiring enormous investment of money and time, with unpredictable return on investment [1]. *De novo* drug development takes around 10 to 15 years, which includes basic discovery, design of medicines, *in vitro* and *in vivo* studies (including safety and efficacy), clinical studies and ultimately market registration of drugs. In contrast, repurposing medication for life-threatening diseases takes only 5-11 years, as many intermediary steps are bypassed if the therapeutic potential of the drug for the disease is confirmed as shown in Fig. (**1**) [8, 9]. This approach provides several benefits over conventional drug development with lower costs in a shorter timeframe with fewer risks, as the effectiveness and safety of the original medication have already been established and approved by regulatory agencies

[4]. In this chapter, we will highlight various drug-repurposing strategies along with therapeutics for repurposing drugs against life-threatening diseases where little or no treatment is available.

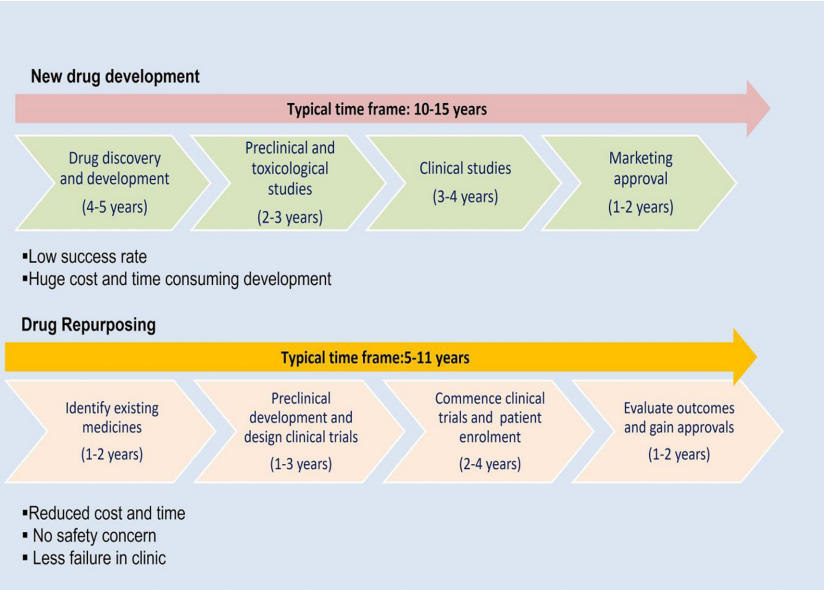

Fig. (1). The approximate time and major steps in the process of *de novo* drug development and repurposing of drugs.

Drug Repurposing Strategies

The primary objective of the drug discovery and development is to establish the therapeutic effectiveness with a very low toxicity-to-benefit ratio. As a result, strategies that use drug candidates with known therapeutic profiles (for drug repurposing) can significantly contribute to the drug development process, thereby reducing development time and costs. Drug candidates with known safety profiles can typically be selected from (a) approved FDA drugs, (b) drugs being studied for a different application, or (c) drugs abandoned or unsuccessful in clinical trials (phase II or III). The success of drug repositioning depends on maximizing therapeutic effectiveness for new targets while reducing off-target effects [10].

Repositioning of drugs is not a new concept, what is new is the ability to do it in a systematic and rational manner rather than relying on serendipity. As the prominence of drug repositioning is gaining practical applications, a number of companies are shifting their focus on developing strategies to make it a systematic exercise. Before moving the applicant drug further down the development

CHAPTER 2

Exploration of Repurposed and Adjuvant Drugs in COVID-19 Patients, as well as Challenges and Ethical Issues Related to Drug Repurposing

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Abstract: The Coronavirus Disease (COVID-19), also referred to as Novel Coronavirus Disease, is a contagious viral disease with a high rate of confirmed cases. Therefore, treatment options are urgently needed to fight the deadly virus. Since there is no standard treatment available, it results in increased morbidity and mortality. The development process of a new drug takes years, so it is crucial to focus on repurposed drugs to reduce the severity of this disease. This review aims to describe the regulatory and molecular aspects of repurposed and adjuvant drugs for COVID-19 based on registered clinical trials and online literature. The use of repurposed drugs brings its own ethical issues and challenges. The challenges of the correct interpretation of existing pre-clinical/clinical evidence and the generation of new evidence concerning drug repurposing in COVID-19 and the issues faced by the repurposing community will also be discussed in the review. When drug repurposing is employed in emergency situations, regional limitations of clinical research ethics, involuntary risk burden, regulatory aspects and ethical issues, fairness in resource distribution for repurposed drugs become an issue that requires careful ethical consideration.

Keywords: Adjuvant drugs, COVID-19, Ethical issues, Repurposed drugs.

INTRODUCTION

The pandemic of Coronavirus Disease (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV2) belongs to the Coronaviridae family of viruses, which is characterized by a high recombination rate that enables it to replicate among animals and humans. Occasionally, recombination in the virus genome within a random host gives rise to a contagious strain, which turns out to be highly pathogenic [1]. The confirmed cases of COVID-19 were heterogeneous and divided into 3 stages; 1) Mild, 2) Severe and 3) Critical cases. Clinical manifestations, such as fever, fatigue and cough, were

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the most common in the majority of cases. Others were myalgia, increased levels of aspartate aminotransferase, C-reactive protein, creatine kinase and creatinine, mostly observed in the complicated cases [2].

Since no standard treatment is available, it results in increased morbidity and mortality. Apart from that, a lack of understanding about drug targets and individual perceptions are adding complications to treating the deadly disease. Therefore, therapeutic plans to counteract COVID-19 infection should be devised. It is very important to evolve a comprehensive understanding of how the virus takes over the host during the infection, and apply this understanding towards the development of both repurposed and adjuvant drugs.

The development process of a novel drug is very complicated, highly expensive and needs 10 to 15 years of research. After the production and designing of the drug, it is also important to examine its pharmacokinetics, pharmacodynamics, toxicity and efficacy in cell and animal-based models [3].

Therefore, exploring effective therapeutic agents to combat COVID-19 is essential and urgent [4]. Therefore, it is very crucial to aim at already available anti-viral and adjuvant drugs to reduce the severity of the disease.

Drug repositioning is a process for the identification of new usage for formerly approved therapeutics and is considered a veritably successful approach for drug discovery because it involves less cost and time to find a remedial agent in comparison to the novel drug discovery process [5]. The molecular pathways of these medicines can also be involved in different diseases. According to a study, 75 percent of formerly approved drugs could be repositioned for the treatment of many diseases [6].

Drug repurposing (DR) can ameliorate the recovery rate by decelerating the replication of COVID-19 contagion and also reducing the symptoms. The Intensive Care Units (ICU) could also be relieved from the pressure by syncopating the time spent by the patients in ICU, which makes it an equal possibility for other patients as well to get the services [7]. Hence, the fastest process to manage the pandemic situation is to repurpose the formerly approved drugs that have been used with a known safety profile [3, 9].

Adjuvant drugs are non-habit-forming, non-opioid medications that can be used as “add-on therapy” to help in the treatment of pain (https://nwapain.com/adjuvant-medications). Frequently used supplements, such as Vitamin-C and zinc, have been reported to decrease the time and seriousness of viral diseases by raising the immune response [8]. The proof supporting supplement therapy as a treatment for infections caused by a virus is very restricted [9]. In the COVID-19 era and

rapidly increasing death rates, there is a desperate need for successful treatment options; whether these supplement molecules could be helpful for the patients infected with the SARS-CoV2 virus is a research question worth assessing [9].

The potential repurposing therapeutics to treat the SARS-CoV-2 infection are anti-malarial, anti-viral, anti-biotic, immunosuppressants, monoclonal antibodies, nti-anthelmintic, ngiotensin-converting enzyme inhibitors, Kinase inhibitors, anti-bacterial, anti-diabetic drugs, anti-tumoral, interferons and others [8].

Potential candidates for adjuvant therapy for SARS-CoV-2 are Resveratrol, stilbene-bases natural compounds, N. Sativa (Black seed), Zinc, HMG CoA reductase inhibitors (statins), Melatonin, Indomethacin, Iron chelators, Vitamin-D, Vitamin-C and others [10].

POTENTIAL CANDIDATES FOR ADJUVANT THERAPY

The potential candidates for adjuvant therapy are summarized below in Table **1**.

Vitamin D

Vitamin D (Vit-D) shows antimicrobial and immunomodulatory activities and is also used as an adjuvant therapy to reduce the consequences of different conditions [11]. According to various studies, people with Vit-D deficiency have a greater chance of developing respiratory infections [12]. When the skin is exposed to UVB rays during the summer season, Vit-D is produced as a secosteroid [13]. COVID-19 severity can be very high in patients with hypovitaminosis (Skin produces less Vit-D in skin) [14]. Research shows that Vit-D plays an important role in balancing the renin-angiotensin system (RAS) and the reduction of lung damage [14]. From a molecular perspective, Vit-D accelerates the differentiation of monocytes into macrophages, enhances leukocyte recruitment and chemotaxis and increases the antimicrobial activity of the innate immune system [15]. It also promotes the production and secretion of defensins and cathelicidin and reinforces the barrier function of different organs [16].

Many studies obtained heterogeneous data by analyzing the role of Vit-D supplementation as treatment and preventive therapy of respiratory infections [16]. However, in most of the clinical trials on paediatric cases, the intervention consists of the administration of 400-1200 IU of Vit-D daily [17]. Therefore, supplements within this range can be advised for COVID-19 prevention.

Stilbenoids

Many plants produce stilbenoids as natural phenolic compounds. They are

CHAPTER 3

Repurposed Drugs Against SARS-CoV-2 Replication in COVID-19

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Abstract: COVID-19 caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV -2), has emerged as a global health problem. It was first reported in Wuhan city of China, in December 2019. Unfortunately, no specific and effective drug is available to treat SARS-CoV-2 infection in patients. There is an urgent need to control COVID-19pandemic. Research & development of novel molecules is a time-consuming and labour-intensive procedure in the midst of a pandemic. The aim of drug repurposing is to find a therapeutically effective molecule from a library of pre-existing compounds. In the present article, a large number of anti-viral drugs with their potential efficacy in inhibiting replication of virus by targeting the virus S protein (Spike protein), 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp) and papain-like protease (PLpro), which play an important role in the replication cycle and pathogenesis of coronaviruses, were assessed as possible treatment options against SARS-CoV-2 infected COVID-19 patients. The continuing SARS-CoV-2 epidemic emphasises the importance of efficient anti-viral medications that can be administered swiftly to decrease morbidity, death, and viral transmission. Several breakthroughs in the development of COVID-19 treatment options might be made by repurposing widely active anti-viral medicines and chemicals that are known to suppress viral replication of related viruses.

Keywords: Anti-viral drugs, COVID-19, Drug repurposing, Remdesivir, Replication, SARS-CoV-2.

INTRODUCTION

COVID-19, a novel coronavirus illness, has become a pandemic danger to human health. It is a respiratory illness that causes dry cough, lethargy, fever, muscular

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pains, and shortness of breath, as well as pneumonia in certain cases [1, 2]. It can induce acute respiratory distress syndrome, which is a severe inflammation of the lung in which fluid builds up within and around the lungs, causing septic trauma owing to a significant drop in blood pressure and the body's parts being underfed for oxygen. This corona virus has an incubation period of 1 to 14 days. The degree of symptoms varies from patient to patient. Due to weakened or damaged immune systems, the elderly, children under the age of six, and individuals with a medical history of asthma, diabetes, or heart disease are especially sensitive to this condition. In December 2019, Wuhan, Hubei Province, China, was the centre of the epidemic [2, 3]. WHO declared this outbreak a Public Health Emergency of International Concern on January 30, 2020, because of its rapid spread and estimated reproductive number (Ro) of 2.2. As of March 20, 2020, it had reached approximately 187 countries (2, 66,073 confirmed cases) and 11,184 confirmed fatalities with a 4.4 ofcase fatality rate (CFT) [4].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19. Middle East respiratory sickness (MERS) virus (MERS-CoV) and SARS-CoV are two more related agents [5, 6]. They infiltrate the pulmonary epithelial cells, deliver their nucleocapsid, and hijack the cellular machinery to multiply in the cytoplasm, attacking the patient's lower respiratory system. The heart, kidneys, liver, gastrointestinal tract, and central nervous system are all affected by the virus family. The Coronaviridae family of enveloped single-stranded, positive-strand ribonucleic acids includes SARS-CoV-2 (RNA) structure.

It is critical to find efficient medicinal chemicals in order to respond quickly to this pandemic viral illness. Presently, due to the urgent need to stop COVID-19 infection, therapeutic approaches for this pandemic include repurposing existing anti-viral drugs that have an effect on the replication of novel SARS-CoV -2 coronavirus [7]. Therapeutic methods for COVID-19 infection patients are divided into two groups based on their targets: (1) medications that target the SARS-CoV-2 life cycle and (2) therapies that have efficacy on the host cells or human immune system. In this chapter, we discuss repurposed drugs with anti-viral effects against SARS-CoV-2 replication, as these substances provide great efficacy for early treatment of COVID-19 by inhibiting the virus life cycle. In addition, it may work as suitable preventive measure, as reported for neuraminidase inhibitors in the influenza virus.

Currently, several clinical trials are ongoing in which many immunomodulators and anti-viral drugs are being investigated for the treatment of COVID-19 patients. These trials aim to decrease the morbidity and mortality rate of this infectious disease until an effective vaccine or drug is developed.

SARS-CoV-2 Genome Structure

The SARS-CoV -2 genome is made up of a single-stranded positive-sense RNA [8]. The SARS-CoV -2 genome was recently sequenced and published to the NCBI genome database (NC 045512.2) with a size of 29.9 kb [9]. SARS-CoV-2 has 13-15 open reading frames (ORFs) with a total of 30,000 nucleotides in its genetic composition. The genome has a GC content of 38 percent and 11 protein-coding genes along with 12 expressed proteins. The genomic organisation of ORFs is strikingly similar to that of SARS-CoV and MERS-CoV [10, 11]. The ORFs are classified as replicase and protease (1a -1b), as well as important S, E, M, and N proteins, in a 5 ′ - 3 ′ order of occurrence and are regarded major drug/vaccine targets. These gene products play critical roles in the viral entrance, fusion, and host cell survival [12]. The SARS -CoV -2 genome is organised in a linear topology, with roughly 89 percent sequence similarity with other CoVs. The translated sequences of SARS-CoV -2 proteins were found in GenBank (Accession ID: NC 045512.2)]. SARS-whole CoV-2's genome encodes a 7096-residue-long polyprotein that contains a variety of structural and non-structural proteins (NSPs). The viral genome's nucleotide content is mostly carried by two non-structural proteins (ORF1a and ORF1ab) and structural proteins. ORFs 1a and 1b encode polyproteins pp1a and pp1ab, respectively, with polyprotein pp1ab encoded *via* the ribosomal frameshift mechanism of gene 1b. These polyproteins are processed by proteinases (virally encoded), which result in the production of 16 proteins that are highly conserved across all CoVs in the same family.

SARS-CoV-2 Infection and Pathogenesis

In COVID-19 infection, SARS-CoV-2 infects its host cells by identifying the angiotensin-converting enzyme 2 (ACE2) enzymes [9]. ACE2 is a transmembrane protein found in the cells of the lungs, arteries, veins, intestines, heart and kidneys [13]. ACE2 operates as a vasodepressor in the pulmonary epithelium, stabilizing the effect of its homologous enzyme ACE1, which behaves as a vasoconstrictor, and both enzymes make up the oxygen-sensitive renin-angiotensin-system (RAS) [14]. The dynamic equilibrium between the expression of ACE1 and ACE2 regulates the RAS system in normoxia. However, in human pulmonary artery smooth muscle cells (hPASMC), ACE1 is upregulated by the hypoxia-inducible factor 1 (HIF-1) (a master regulator of the response to hypoxia) during chronic hypoxia (oxygen 2 percent for 12 days), but ACE2 expression is significantly reduced [15]. Similar results were found in male rats exposed to altitudes of 4,500 metres, which revealed higher levels of ACE1 and reduced expression of ACE2 in cardiac cells after 28 days [16]. As the level of expression of ACE2 (in pulmonary epithelial cells) has been shown to be certainly correlated with the rate of SARS-CoVinfection [9, 17 - 19], these findings are extremely important for the

CHAPTER 4

Targeting the Viral Entry Pathways through Repurposed Drugs in Sars-Cov-2 Infection

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Abstract: SARS-CoV-2 belongs to the family coronviradae and the disease caused by this virus is known as COVID-19. Viral entry into the cell is favored by spike glycoprotein, which interacts with Angiotensin-converting-enzyme-2 (ACE-2). Moreover, proteins such as Transmembrane Protease Serine-2 (TMPRSS-2), are responsible for viral fusion with cellular epithelium. Traditional drug discovery methods and their development process are time-consuming as well as expensive. Thus, there is a need for a method that can overcome such drawbacks. Drug repurposing is an approach in which we can use an existing drug that is already being used for another disease. The repurposing of drugs is also known as repositioning. It is the process that identifies new therapeutic use for existing or available drugs. Hydroxychloroquine inhibits ACE-2 glycosylation virus entry to the host body; arbidol prevents fusion of viral lipid shell with cell membrane hence restricting contact and penetration of virus. Drug repurposing could be a successful strategy for the treatment of sporadic, neglected diseases, difficult-to-treat diseases, and the current pandemic situation, *i.e.*, COVID-19. However, there is no denying the fact that there are several limitations to this approach.

keywords: Animal model, Antiviral, Computational approach, COVID-19, Drug repurposing, Experimental approach, Phytochemicals, SARS-CoV-2 Spike Protein, Viral inhibition.

INTRODUCTION

COVID-19 is caused by the infection of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). This virus belongs to the Nidovirales order family coronviradae and has two subfamilies, Coronavirinae and Torovirinae. As the name suggests, it affects the respiratory system mainly. This virus spread like a

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fire in the jungle worldwide and became a pandemic leading to multiple infections and several deaths occur due to this virus. The general symptoms of people infected with SARS-CoV-2 are cough, chest discomfort, dyspnea (Which occurs in the majority of people), and symptoms that are related to gastrointestinal discomforts like vomiting and diarrhea (Which occur rarely). The immune system also gets affected; there will be a decrease in the lymphocyte count. It affects the major vital organs of the body lungs, heart, and kidneys. It is found that people infected with SARS-CoV-2 showed glassy opacity in the lungs. In clinical chemistry, it is found that there is an increase in the alanine transaminase, lactate dehydrogenase, and D- dimer count [1, 2].

Viral entry is by various proteins and enzymes (Figs. **1** and **2**). The envelope-embedded surface-located spike (S) glycoprotein is responsible for coronavirus entrance. Most of the time, host proteases will cleave this S protein into the S1 and S2 subunits, which are important for receptor identification and membrane fusion. S1 is further separated into two parts: an N-terminal domain (NTD) and a C-terminal domain (CTD), both of which serve as receptor-binding entrance points. SARS-CoV and MERS-CoV, for example, use the S1 CTD to detect receptors (also called receptor binding domain). The spike protein of SARS-CoV-2 interacts with the Angiotensin-converting-enzyme-2 (ACE-2) receptor of the host cell (S). ACE-2 is an enzyme that breaks down the bigger protein angiotensinogen to produce tiny proteins that control cell activity. Angiotensin II (ANG II) can cause inflammation and the death of cells in the alveoli, which are important for delivering oxygen to the body; ACE-2 counteracts these negative effects of ANG II. The SARS-CoV-2 virus attaches to ACE-2 stops it from regulating ANG II signaling. As a result, the activity of ACE-2 is blocked, erasing the gaps in ANG II signaling and allowing more ANG II to reach injured tissues. In covid19 patients, this reduced breaking is expected to harm the lungs and heart. Another enzyme such as Transmembrane Prot Transmembrane Protease Serine-2 (TMPRSS-2) is encoded by the TMPRSS-2 gene in humans. TMPRSS-2 is a cell surface protein produced largely by endothelial cells in the respiratory and gastrointestinal systems. It functions as a serine protease, cleaving peptide bonds in proteins with serine as the nucleophilic amino acid at the active site. SARS-CoV-2 and other coronaviruses require TMPRSS-2 to enter the body. By binding to ACE-2, TMPRSS-2 activates the spike protein domain (a glycoprotein present on coronaviruses), causing the virus to fuse to the respiratory epithelia on the cell surface in case of non-endocytic entry. Cathepsin L is a cysteine protease that shows its best activity in a slightly acidic medium. Without cleavage of spike protein by this protease, the virus can not enter the cell; this process occurs when the virus follows endocytic entry. In addition, refer to Table **1** for brief information regarding the various variants of SARS-CoV-2.

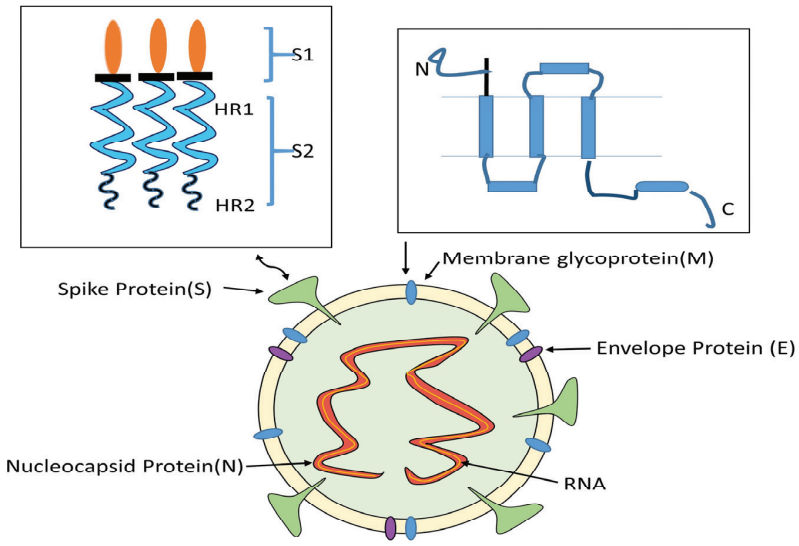

Fig. (1). Illustration of SARS-CoV-2 biological structure. S proteins of the coronavirus from their crown-like appearance. S proteins are cleaved by furin or related enzyme into S1 and S2 subunits in the Golgi complex region. The M-protein is composed of three parts, a short N-terminal domain (situated outside the particle), three transmembrane domains, and a carboxy domain (situated inside the particle).

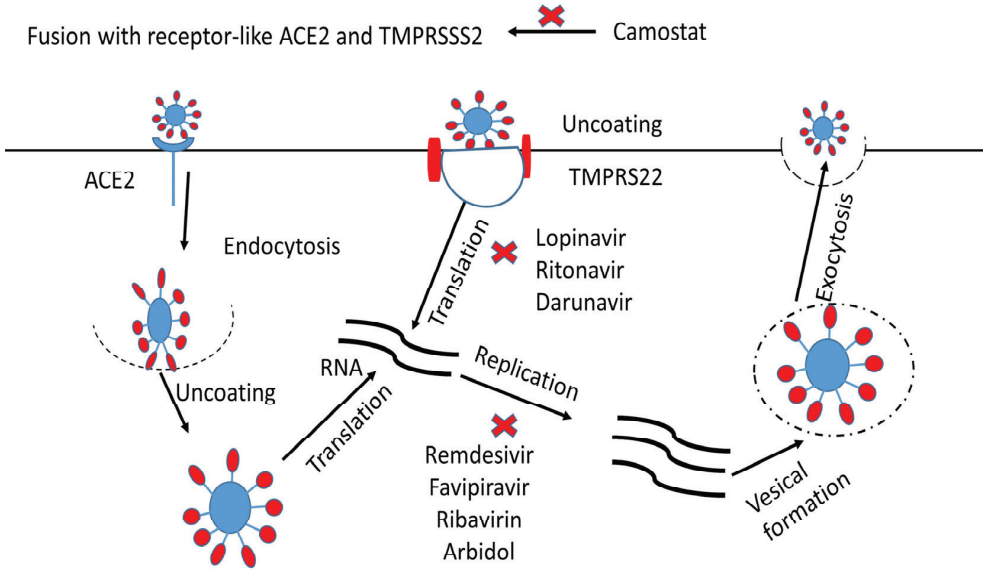

Fig. (2). Illustration of the mechanism of virus uptake inhibition by various repurposed drugs.

CHAPTER 5

Repurposed Drugs/Potential Pharmacological Agents Targeting Cytokine Release and Induction of Coagulation in COVID-19

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Abstract: Global public health has been challenged by the coronavirus 2019 (COVID-19) and has been a threat to clinical management to fight this viral infection. Due to the lack of specific therapies, there is a race among the scientific fraternity to find its specific cure to date. COVID-19 symptoms range from mild fatigue to potentially fatal pneumonia, cytokine storm (CS), and multi-organ failure. Hence, investigating the repurposing of current medications for use in the management of COVID-19 patients is a realistic approach. It is prudent to investigate using repurposed medications in the management of COVID-19 patients. In the meantime, researchers are testing a number of antiviral and immunomodulatory medicines to combat the infection. Although antiviral as well as supportive medications are undoubtedly vital in the treatment of COVID-19 patients, anti-inflammatory agents play an essential part in COVID-19 patient care due to their potential to prevent additional injury and organ damage and/or failure. Moreover, COVID-19-mediated infection can be linked with coagulopathy. The most common thrombotic events in COVID-19 are venous thromboembolic (VTE), which are linked with increased severity of disease and poor clinical outcomes. Here, we evaluated medicines that potentially modulate pro-inflammatory cytokines and assist in COVID-19 management. We emphasized various pro-inflammatory cytokines as targets of repurposed drugs and targeted induction coagulation in COVID-19 patients using the available literature and studies.

Keywords: Anticoagulation, Coagulopathy, Cytokine storm, Interleukin-1, Interleukin-6, Pro-inflammatory cytokines, Repurposed drugs, SARS-CoV-2, Thrombosis, Tumor necrosis factor.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has posed a significant threat to global public health. It was first reported as some unknown pneumonia cases in Wuhan, Hubei province, China, in December 2019. Still, we are competing with a different and new variant of the coronavirus to survive. This pandemic is one of the most difficult to control crises in the history of the world. The lives of millions of people are threatened, and many more are still fighting this virus lurking in the atmosphere [1, 2]. Due to this unprecedented mortality and morbidity rate, it is the need of the hour to identify potential targets and repurpose drugs as therapeutic options for this disease. Meanwhile, the scientific community is working tirelessly to find a specific cure for this disease. In this critical situation, drug repurposing is not only fast but also a feasible approach to analyse potent medications for fighting this infection with minimal side effects. We should know the structural analysis of drug target proteins and the pathogenesis of SARS- CoV-2 infection to develop therapeutic approaches [3].

Coronaviruses refer to the family Coronaviridae, subfamily *Coronavirinae,* and of the order *Nidovirales,* as per the International Committee on Taxonomy of Viruses. Further, the Coronavirinae subfamily is grouped into 4 genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus,* and *Deltacoronavirus* [4]. SARS-CoV-2 belongs to the betacoronavirus genera (subgenus sarbecovirus). Alpha and Beta Coronaviruses can infect mammals, while Gamma and Delta CoV are able to infect birds [5]. Earlier in the past two decades, two other zoonotic strains of coronaviruses caused severe respiratory illnesses, namely, severe acute respiratory syndrome coronavirus (SARS- CoV) as well as Middle East respiratory syndrome coronavirus (MERS), began to spread globally. In the years 2002 and 2003, SARS- CoV was the cause of severe acute respiratory syndrome (SARS) outbreaks in China, having a mortality rate of 10%, while MERS-CoV emerged in the year 2012, originating from the Arabian peninsula as an epidemic outbreak. The case fatality rate of MERS was much higher (around 35%) than SARS-CoV, while the basic reproductive number of MERS (R_0) was approx 1. It means the infected person can transmit the disease to up to one person [6 - 8].

SARS-CoV-2 is contagious and spreads mostly by respiratory droplets, with a high transmission rate in the first week of infection. The diagnosis of COVID-19 is carried out by a reverse transcription polymerase chain reaction (RT-PCR) test for coronavirus detection. It was observed that people affected by COVID-19 showed a peak viral load in the first week of illness that gradually decreased by the next week. COVID-19 is now known as a disease that can be associated with multi-organ disorders and a broad spectrum of clinical symptoms [6, 8].

Metagenomic RNA sequencing data of the SARS-CoV-2 unveiled 96.2% analogy to bat-CoV Ra TG13 and 79.6% sequence identity to SARS-CoV [9]. Due to this close phylogenetic similarity, bats were supposed to be the natural host of this virus [9].

This chapter briefly discusses the structure, mutation, and pathogenesis of SARS-CoV-2. Moreover, pro-inflammatory cytokines, cytokine storm (CS), COVID-19-associated CS, and pro-inflammatory cytokines as targets of repurposed drugs were presented. Moreover, we have conferred targeting induction of coagulation in COVID-19 patients.

MECHANISM OF PATHOGENESIS IN COVID-19

SARS-CoV-2 Structure and Mutation

SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus [10 - 12]. SARS-CoV-2 is characterised by 4 structural proteins- spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, which are primal for infectivity and replication [13 - 17]. There are six functional open reading frames (ORFs) which are arranged in order from 5′ to 3′: replicase (ORF1a/ORF1b), spike, envelope, membrane, and nucleocapsid [10]. The S protein consists of two subunits-S1 and S2. When S protein bulges from the membrane side, it gives the virus its appearance [18]. The S protein tip has a crowned (Latin corona) structure [18]. Also, the S protein is essential for binding to the angiotensin-converting enzyme 2 (ACE2) receptor, the key point where the virus enters the human body as well as the animal host [19]. In addition, S protein is the main player in immunogenic response and target of vaccines [19, 20]. M protein (~25-30kDa) is a transmembrane protein essential in viral pathogenesis [21]. S2 portion is highly conserved, and it helps in cell membrane fusion [21]. The E protein (8-12 kDa) is poorly understood, but it is supposed that it has a role in viral replication and infectivity [22, 23]. The N protein is involved in viral RNA replication, transcription, and synthesis control [24]. SARS-CoV-2 also features a hemagglutination-esterase (HE) dimer in structure, that binds to sialic acid and reflects esterase activity to aid viral S-protein cell entrance and propagation [25].

Evidence shows that there are unique mutations in the SARS-CoV-2 [26]. SARS-Co-V-2 mutant variants are as follows: UK variant (B.1.1.7), Brazilian variant (P.1) and South African variant (B.1.351) [27, 28]. The main mutation regions (of these variants) are located in spike protein. B.1.1.7 variants are more contagious and spread faster, which may be related to how well they bind to the ACE2 receptor [27, 29].

CHAPTER 6

High Throughput Screening (HTS) Methods for Screening of Known Drugs for COVID-19

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Abstract: The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 has triggered an ongoing global pandemic whereby infection may result in a lethal severe pneumonia-like disease designated as coronavirus disease 2019 (COVID-19). Thus, the repositioning of known drugs can significantly accelerate the development and deployment of therapies for COVID-19.

High throughput screening (HTS) is the use of automated equipment to rapidly test thousands to millions of samples for biological activity at the model organism, cellular, pathway, or molecular level. In its most common form, HTS is an experimental process in which 10^3–10^6 small molecule compounds of known structure are screened in parallel. Currently, this technique is being used to screen known compounds in several diseases, including COVID-19. In the current scenario, it is important to focus on the application of high-throughput screening (HTS) in the drug discovery process.

In this chapter, we have covered methods of the high-throughput screen and its use in screening known drugs against infectious diseases like COVID-19. Moreover, the challenges and future of these technologies have been focussed.

Keywords: COVID-19, Drug discovery, High Throughput Screening, SARS-CoV-2.

INTRODUCTION

A clinical condition or a disease in the body leads to the initiation of drug discovery. The unmet clinical need provokes the discovery of the drug. The process of drug discovery starts with a 'hypothesis' that is the result of initial research. The hypothesis may include activation or inhibition of any protein, enz-

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yme, or metabolic pathway. The hypothesis later resulted in a therapeutic effect in a disease state [1]. Drug discovery is a highly complex, tedious and multidisciplinary process, and its ultimate goal is to recognize new drugs with desired characteristics. A single marketed drug emerges from approximately a million screened compounds. For this, large compound libraries are screened. The process of drug discovery starts with the identification of suitable drug targets, which includes molecules such as enzymes and receptors, at times, ion channels also. Enzymes such as kinases, phosphatases, proteases and peptidases are the most common targets of HTS [2]. The next step is the target validation which is done *in vitro* and *in vivo* on animals. The ultimate validation is achieved in humans. Fig. (**1**) shows the entire process of Drug discovery. The modulators may be in respect to the target, such as agonist or antagonist, while in the case of receptors, it may be an activator or an inhibitor [3].

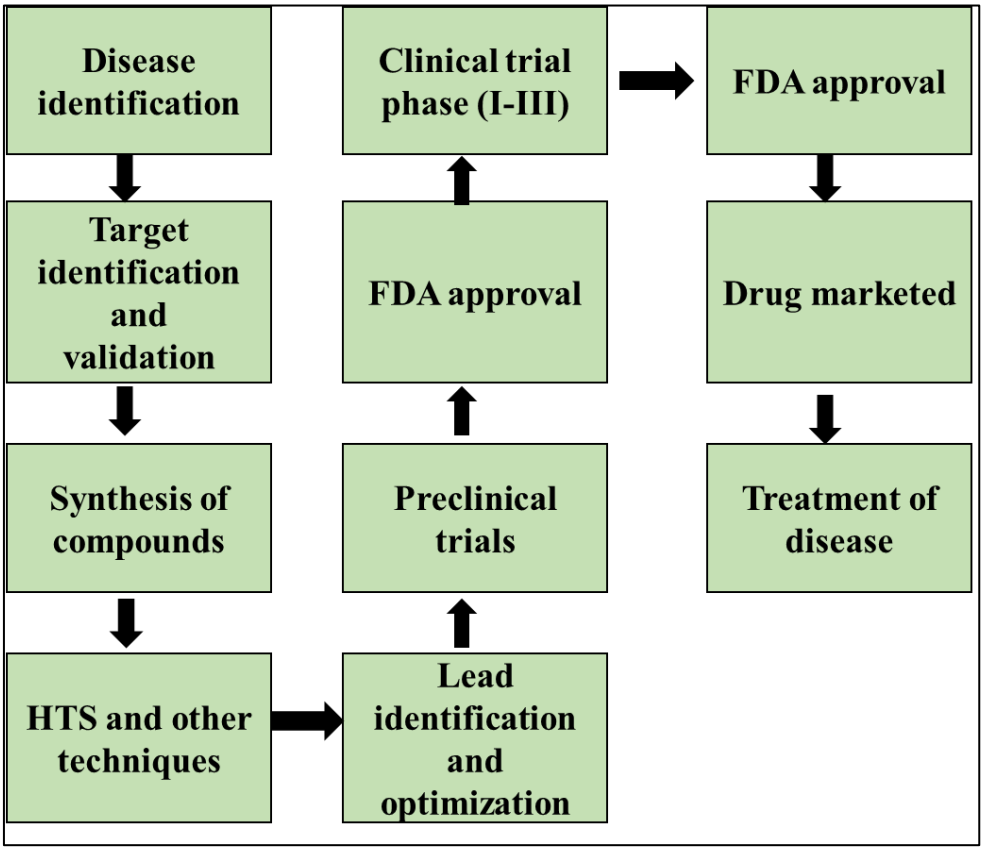

Fig. (1). Flowchart showing the process of drug discovery.

Hit identification and lead optimization are very much intertwined with computational modelling [4]. The ultimate goal of target validation leads to "lead identification". For the purpose of target validation, various suitable assays are designed and developed. HTS exposes the target to various compound libraries in order to get lead identification. The selection of lead identification depends on selectivity, pharmacokinetics and physicochemical properties [3].

High Throughput Screening

High throughput screening is one of the most important method for the discovery of drugs in this modern technological world. It is used to identify "hits" from known compound libraries that might become a "lead" compound for optimization of the drug in the future. HTS is the first step in the search for an active compound with the potential to develop into an active compound.

This technology relies on various other branches of science, such as bioinformatics, combinatorial chemistry and parallel synthesis approaches. The ability to test a huge number of compounds quickly and efficiently provides a competitive opportunity, making HTS a crucial tool in many pharmaceutical companies which exploits this technique for the discovery of the drug [5]. Bioinformatics, genomics and proteomics help in the identification of novel biological targets that are related to the disease. The parallel synthesis approach and combinational chemistry yields a large number of small compounds which are already available for the purpose of drug discovery.

The primary purpose of screening is to search the compound libraries and recognize a compound that has desired characteristics and could interact with the selected system in a proper way. For this purpose various compounds are being assayed against the target in order to get a specific mechanism of action for *e.g.*, in the case of an enzyme, its activation or inhibition by the compound or its receptor-ligand interaction. The compound of interest with all the desired activities is recognized and is then allowed to undergo different biological assays in order to optimize the efficacy and drug-like properties. The refinement/processing of the compound properties is known as "hit" to "lead" process. The ultimate goal of the screening is to develop a drug candidate with desired characteristics which could be further used for optimization and development of a new drug useful in the treatment of the disease [6]. The inverted pyramid in Fig. (**2**) shows how the ultimate compound of interest is achieved.

CHAPTER 7

Drug Repurposing for COVID-19 using Computational Methods

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Abstract: In this chapter, we use computational methods to illustrate drug repurposing with the example of COVID-19. Here, the current status of drug discovery has been described with various aspects of drug repurposing interactions, use of algorithms in drug repurposing, re-evaluation of existing drugs, challenges in drug repurposing, and biological and computational interpretation of personalised and AI-guided repurposing. In addition, we present blueprints for pacing up the drug repurposing process using artificial intelligence. This chapter is devoted to the use of computational intelligence for drug repurposing against various diseases, including COVID-19.

Keywords: Artificial intelligence, Computational methods, COVID-19, Drug, Repurposing.

INTRODUCTION

Multiple drugs have been developed for various diseases [1]. The majority of them were discovered by serendipity. This process developed a huge collection of approved drugs, which provides an opportunity to rethink the purposes of drugs in various human physiological statuses. In today's scenario, re-thinking about the purpose of drugs is termed "Drug repurposing" [2]. It is a thematic terminology, representing a way of working for identification of those suggestive clues, which can provide a strong ground for rethinking the purpose of exiting or pipelined drugs. The back force for such repurposing comes due to the bonus benefit of getting rid of a major part of clinical trials; which may become very supportive for saving time & money, as well as approaching new prescriptions to the patients in a very cost-effective manner [2]. The theme of repurposing is not new; for decades, researchers have already been devoted to reviewing the aspects of

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existing drugs for various utilities. In this way, research outputs from previous studies became the ground for cultivating the idea for the identification of additional usage of previous studies [3].

Multiple reports are available, which show the success story as well as existing challenges regarding drug repurposing. Success represents the power of drug repurposing for fast drug identification for newly developing diseases, also useful for searching for solutions in pandemic situations. But, background information about molecular interactions with newly developing drugs is always challenging. Because molecular interactions follow relative behavior, a complete set of a system of molecular components is required to understand the behavior of each drug molecule. For such types of studies, the genomic ground is required to agitate the combinations of system properties to extract significant therapeutic interpretations. On the coarse side of such observations, attempts have been implemented with various interactomes to understand and interpret computational drug development. To handle the complexity of data analysis, algorithms from artificial intelligence were used for drug repurposing. These efforts of understanding the interactions are used for finding the hidden aspects, as well as unravelling the possible links among various drugs, targets, and human diseases. Such clues become very important for resolving possible drug repurposing. This seems possible because of the sharable functional behavior of protein-protein interactions, which shows that drug targeting for one disease may resolve another too [4].

About Data Size & its Handling with Computational Methods: Long-term experimental practices, dumped huge electronic data. Using such large data for rethinking any drug based on stored experimental data, the existence of false negatives is quite feasible. Therefore, handling big data requires high-end applications of information technology. In the mid-19th century, researchers had forecasted computational methods as an approval ground for human interpretations. These enhancements are only possible with artificial intelligence. When we consider forecasting for repurposing, AI dependencies also come into existence. Computation for such machine intelligence requires a high computation capacity of processors as well as high storage capacity. Concrete establishment in artificial intelligence, based on the novel wealth of data, is only feasible with high processing and storage capacity. Now it is well known that artificial intelligence is being implemented in diverse areas of research as well as technological developments in the area of data mining. Artificial intelligence is also revolutionizing the area of drug discovery by exposing patterns from biological data. The existing R&D units use artificial intelligence for computational drug discovery and development. These technologies define diseases and their therapeutic aspects with minimum error [5].

This chapter introduces methods implemented for drug repurposing in general. Specific explanations of drug-repurposing were also provided with examples of COVID-19. Here, we discuss the current status in drug discovery, approaches already implemented for drug repurposing, computational methods used in drug repurposing, information about possible existing drugs used during pandemic conditions, challenges faced during drug repurposing, Biological and non-biological criteria for handling personalized and Artificial Intelligence-guided repurposing. We also attempted to present a clear picture of the possible utilization of AI for speeding up drug repurposing. This chapter provides a strong rationale for drug repurposing against various human diseases, including COVID-19.

CURRENT STATUS OF DRUG-REPURPOSING

Drug repurposing is one of the enhancing ways of identifying new therapeutic molecules. Diversified utilization of various methods has been implemented for the discovery of drugs in the most efficient way. Methods used involve structure-based processes for the identification of drugs, *i.e.*, involving structures of ligands and proteins. Now the question arises of how to relate the combinations of structures for drug-repurposing. The point of attention is that the purpose of drugs can be represented by either structure of drug, or structure of protein, or both. The reason behind this is that here, repurposing is dependent on the known structures (*i.e.*, drugs and proteins) and their biological functionality. That means any type of link between drug and protein will present their existing relationships as in any standard network. Therefore, if our analysis process somehow re-establishes links between the drugs and proteins, then it will represent the repurposing of drugs. Now, the question arises, how many ways can present the interactions of drugs & proteins. Ultimately by implementing the structure-functionality linking, we have to perform a screening process for drug repurposing. Till now, docking followed by molecular dynamics-based virtual screening was the method for structure-function-based screening. Now, big-data-based structure-functionality linking has become the evolving method for establishing an efficient way for screening molecules for possible functionalities. Here, we will discuss the linking-based content for drug-repurposing-based methods one by one [6].

Repurposing Through a Drug-drug Interaction Network

One way to observe drug repurposing may be the observation of drug-drug interactions. This process is based on pharmacological functions (PhFs). PhFs can be used as selective behavior of drugs for specific purposes because drugs with similar PhFs will be compactly clustered at one centroid, while non-clustered drugs may be picked for suitable re-purposing. These PhFs can be defined based

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