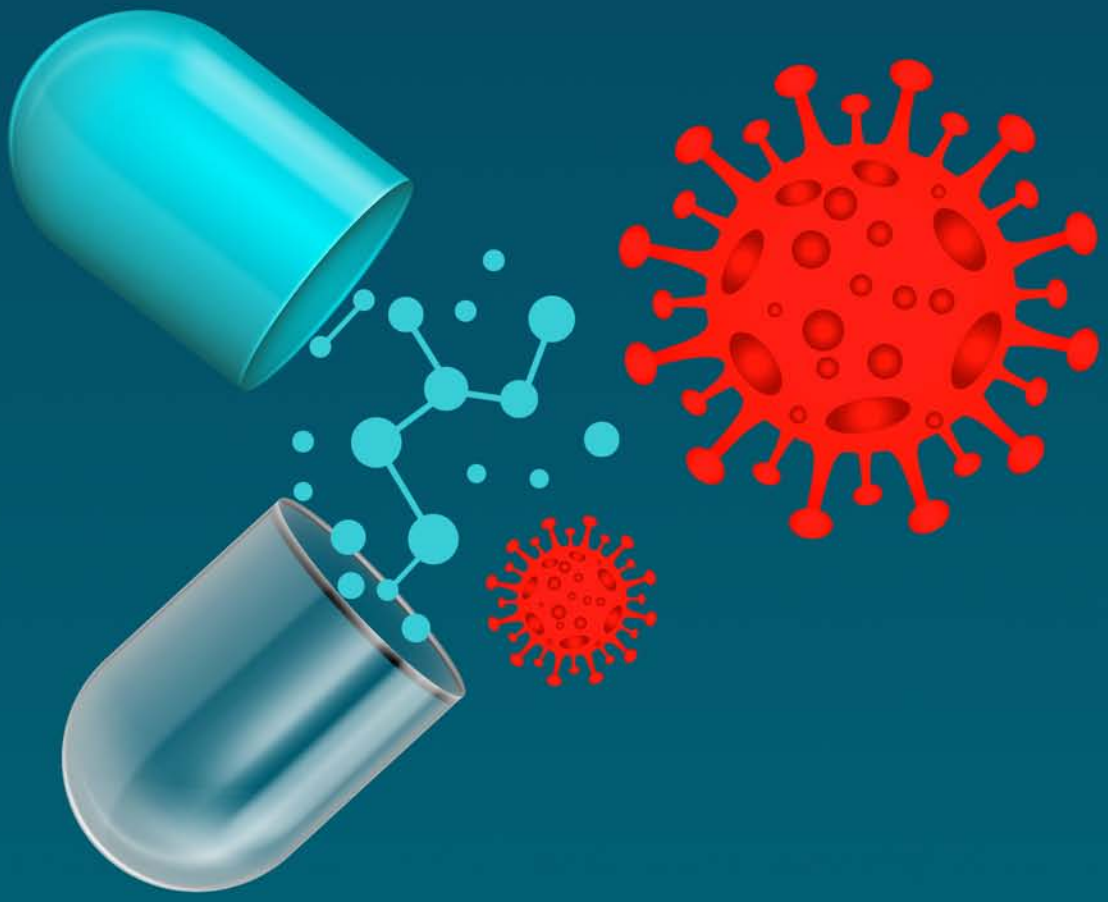
DRUG REPURPOSING FOR ANTIVIRALS



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PREFACE

In the ever-evolving landscape of medical science, the quest for effective antiviral therapies stands as a paramount challenge and an imperative for the well-being of humanity. As we navigate the complexities of infectious diseases, the concept of repurposing existing drugs emerges as a beacon of promise—a testament to our capacity for innovation and adaptability.

This preface serves as a contemplative gateway into the realm of drug repurposing for antiviral therapy, a subject that bridges the realms of discovery, translational research, and clinical application. As we embark on this exploration, it is essential to acknowledge the multifaceted nature of our endeavour.

The backdrop of drug repurposing is painted against the canvas of scientific serendipity and the constant evolution of our understanding of pharmacology. It is a narrative that celebrates the unexpected, where the drugs that are developed for one purpose reveal an unsuspected potential in the realm of antiviral defence. This approach is emblematic of our capacity to extract novel solutions from the familiar, propelling us toward faster, more cost-effective responses to viral threats.

The purpose of this exploration goes beyond the immediate need for antiviral interventions. It is a strategic response that leverages the wealth of pharmacological knowledge accrued over decades. As we delve into the diverse mechanisms of action inherent in repurposed drugs, we anticipate not only immediate solutions to pressing health challenges but also the seeds of innovation that may blossom into broader therapeutic strategies.

This compendium is a collaborative effort that brings together insights from researchers, clinicians, and pharmaceutical pioneers. It seeks to unravel the potential of drug repurposing by examining the nuances of molecular interactions, clinical trials, and the intricate dance between viruses and therapeutic agents. Through the chapters that follow, we embark on a journey that not only sheds light on the present state of antiviral repurposing but also looks forward to the untapped possibilities that lie on the horizon.

As we turn these pages, may we find inspiration in the resilience of scientific inquiry, the ingenuity of drug repurposing, and the collective commitment to safeguarding public health. May this compendium serve as both a guide and a catalyst for further exploration, fostering a community of thinkers and doers dedicated to advancing the frontiers of antiviral therapy.

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CHAPTER 1

Introduction to Drug Repurposing for Antiviral Therapy

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Abstract: Multiple deaths result from infections caused by viruses worldwide. In recent years the world has experienced multiple outbreaks of viral diseases that were once considered harmless. These diseases have been ignored for a long time, and there are no approved medications or vaccinations, leaving the pharmaceutical industry and various research groups running out of time to find new therapies or prevention strategies. Developing new antiviral compounds costs $350 million to $2 billion, and it takes 10-15 years for the compound to transition from medical labs to clinics worldwide. Increased interest in medication repurposing methods has emerged to address these shortcomings. New drug repurposing strategies have significantly reduced the rate of failure, which was previously around 92%. Since it uses safe pharmaceuticals, medication repurposing is rapid and cost-effective. This chapter focuses on recent developments in identifying broad-spectrum antiviral drugs through repurposing existing medications. It was determined that there are two basic groups of repurposed antivirals: direct-acting antivirals (DARA) and host-targeting antivirals (HTRA). Specific categories were used to highlight a variety of approaches to repurposing medications for the treatment of viral infectious diseases such as Ebola, ZIKA, dengue, influenza, HIV, HSV, and CMV, amongst others. Drug repurposing is a promising way to generate novel antiviral drugs swiftly for addressing challenges in antiviral treatment, and it is one of the most efficient methods that can be used. The outcomes of pharmacological repurposing that present the most favorable outcomes for the treatment of infectious diseases are presented in this chapter.

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Keywords: Antiviral drugs, Pharmaceuticals, Repurposing methods, Virus therapy, Viral diseases.

INTRODUCTION

Drug repurposing, sometimes called drug reprofiling or drug repositioning, involves studying the molecular characteristics of current drugs to discover new uses for treating other health conditions. In light of the high failure rate of approximately 90 percent and the large cost associated with the production of new medications and combinations, researchers are concentrating more of their attention on the process of drug repurposing. Through the utilization of this method, the danger of failure is decreased as a result of the prior certification of the medications for translational use in individuals suffering from a variety of conditions. This, in turn, reduces the possible toxicity that is linked with these medications [1]. This technique has the potential to significantly cut down on the amount of time required for preclinical evaluation, clinical trials, and the development of various pharmaceutical formulations based on the Structure-Activity Relationship (SAR). As a further benefit, the potential reduction in testing time could make it possible for us to immediately deliver effective medicine formulations to communities and areas around the world that are affected by the epidemic [2].

Viruses are a diverse group of pathogens that can lead to severe diseases. Over the past three decades, several antiviral medications focusing on viral proteins or host-related factors have been effectively developed. The need for new antiviral drugs is motivated by persistent viral diseases such as HIV, influenza, and hepatitis C, as well as the appearance of new infections like picornaviruses and coronaviruses. Resistance to current antiviral medications is also a contributing factor. Studying the molecular mechanisms of infection has resulted in the creation of novel antiviral drugs that focus on different viral proteins and host factors. Research is focused on identifying novel targets and processes to generate new antiviral drugs to treat chronic infectious diseases and combat increasingly efficient viruses. Between 2012 and 2017, the FDA authorized 12 new antiviral drugs in the USA, with 8 for Hepatitis C Virus (HCV)-related conditions and 2 for HIV drug combinations [3, 4]. The World Health Organization (WHO) and governments of the world are worried about the global risk posed by emerging and re-emerging viruses that have led to past outbreaks. Several infectious diseases, such as Zika virus (ZIKV), Ebola virus (EBOV), Middle East Respiratory Syndrome Corona Virus (MERS-CoV), and other emerging viruses do not have available treatments [5 - 7]. Despite the fact that it is not a unique method, drug repurposing has been increasingly popular in the process of developing therapeutic options for the purpose of countering the morbidity and

mortality that are caused by viruses such as the Human Immunodeficiency Virus (HIV) and the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co--2). This strategy has been utilized to create more effective medications and has facilitated the production of different drugs for novel uses. In addition to being used as antiviral agents, the process of repurposing pharmaceuticals is being extensively studied to develop treatments for emerging infections [8, 9]. A comprehensive grasp of pharmacokinetics and pharmacodynamics is required in order to evaluate new applications for medications that have already been approved. In order to acquire a comprehensive understanding of the pharmacological selection process for the new purpose, a huge amount of data from Phase IV and post-marketing studies is available [10]. For the purpose of achieving rapid and accelerated licensing of pharmaceuticals during pandemics, Giovannoni *et al.* evaluated policy-focused methods for drug repurposing and brought attention to the critical significance of post-marketing research. Pharmaceutical businesses often prioritize post-marketing evaluations in Life Cycle Management (LCM) to prolong the patent life of their medicines. Over time, these inquiries are found to be quite beneficial for adapting current drugs for new purposes [11].

Origin of Repurposing

The scientific literature has several studies aiming to determine the effectiveness of using a drug for a different medical condition. However, the website http://drugrepurposing.info lists just 94 instances when a repurposed drug was successfully brought to the market (retrieved on January 3, 2018). The global sales of repositioned pharmaceuticals reached $250 billion in 2014, which is equivalent to approximately 25 percent of the annual revenue earned by the pharmaceutical sector. Within their newly approved applications, five of these treatments generated revenues of more than one billion dollars [12]. Repurposing can be achieved by discovering new compounds based on their phenotypic benefits without needing to define their method of action explicitly. The results are more useful for medical usage and research because they may be examined directly in preclinical animal models. It has the potential to progress directly to Phase II clinical trials. The risk of failure associated with repurposed medications is negligible. Fig. (**1**) highlights the distinction between conventional drug development and drug repurposing [13].

Bayer first introduced aspirin as a pain reliever in 1899. It was later reintroduced in the 1980s as a drug that prevents blood platelets from clumping together, but only when taken in small amounts. Vane's research resulted in him being given the Nobel Prize in Medicine in 1982, and it is still frequently used today for the purpose of reducing cardiovascular issues. It was discovered by Dr. Lawrence

CHAPTER 2

Case Studies in Antiviral Drug Repurposing

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Abstract: The incessant emergence of novel viral pathogens poses a perpetual challenge to global public health. Traditional drug development pipelines often lag behind the urgent need for effective antiviral treatments. In this context, drug repurposing has emerged as a promising strategy to expedite the identification and deployment of therapeutics against both known and novel viral infections. This article explores the concept of drug repurposing in antiviral therapy, highlighting its potential to harness existing pharmaceutical agents for novel indications. By leveraging the extensive knowledge of drug safety profiles, pharmacokinetics, and mechanisms of action, repurposed drugs offer a shortcut to clinical trials and regulatory approval, thereby accelerating the time to market. Furthermore, drug repurposing provides a cost-effective approach compared to de novo drug discovery and development. This article reviews successful examples of drug repurposing in antiviral therapy, such as the use of nucleoside analogs originally developed for other viral infections like HIV and hepatitis C, now being repurposed for emerging viral threats such as SARS-CoV-2. Additionally, it discusses the challenges and limitations associated with drug repurposing, including issues related to intellectual property, off-label use, and the need for robust preclinical and clinical evidence. Overall, drug repurposing presents a compelling avenue for the rapid response to emerging viral outbreaks, offering a pragmatic and resource-efficient approach to combat the evolving landscape of infectious diseases.

Keywords: Artificial intelligence, Chloroquine, Drug repurposing, Ivermectin, Machine learning, Pathogens, Remdesivir triphosphate, Virus.

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INTRODUCTION

Drug recycling, also known as medication rediscovery, drug repositioning, drug refiling, and drug redirection, is a tactic for finding new uses for authorized medications in medical indications outside of their original intended uses [1]. The process of developing new drugs takes money and time. Repurposing current medications for novel therapeutics is a compelling approach that lowers trial costs while speeding up drug development [2]. Additionally, it is regarded as a suitable approach for discovering drugs for uncommon and orphan diseases [3]. Drug repositioning is based on two fundamental scientific discoveries: a.) the idea of pleiotropic medications and b) the realization that certain diseases have biological targets that are occasionally shared, as demonstrated by the deciphering of the human genetic code [4]. Given the substantial failure rate (about 90%) and enormous resources needed to discover new medicines and their combinations, the scientific community is closely monitoring the prescription repurposing technique [5]. Medication repurposing is thought to be able to cut the 10-17 year medication growth process down to 3–12 years. Remodelling drugs is said to account for 10 to 50 percent of a pharmaceutical company's research and development expenditures [6].

Rationale Behind Drug Repurposing

Viruses pose a continuous risk to people, pets, and vegetation. There are hundreds of viruses that can infect people and cause illness, but the majority of them have no known cure. Public health is concerned about viruses that are resurfacing or developing. These pathogens include the following: Zika virus (ZIKV), Crimean Congo Haemorrhagic Fever Virus (CCHFV), Severe Fever Thrombocytopenia Syndrome Virus (SFTSV), Chikungunya Virus (CHIKV), Ebola Virus (EBOV), Dengue Virus (DENV), West Nile Virus (WNV), Yellow Fever Virus (YFV), and Influenza A Virus (IAV) [7]. Globally, the COVID-19 pandemic condition is continually changing. The worldwide medical disaster known as the COVID-19 pandemic is caused by the coronavirus SARS-CoV-2. The one-stranded positive-sense RNA viruses known as coronaviruses have a genome that is roughly 30 kb in size and encodes a few key structural proteins [8]. Drug repurposing is a different approach to drug development that has gained traction due to the slow pace of innovative drug discovery, high attrition rates, and rising regulatory barriers [9].

Importance of Drug Repurposing in Antiviral Therapy

Repurposing pharmaceuticals has gained popularity as a quick and efficient method of identifying medications to prevent the spread of newly discovered infectious diseases, particularly viral infections [10]. The effectiveness of

developing medications that target host factors and viral proteins is limited by the advent of resistant viruses and their unfavourable side effects. The process of finding new uses for drugs with FDA authorization that are currently on the market is known as "medication recycling", and it is a potential means of quickening the pace at which treatments for infectious diseases and numerous other ailments are developed. In the fight against the numerous terrible diseases that are spreading quickly, including HIV, influenza, hepatitis C, Ebola, dengue, and many more, drug repurposing is crucial [11]. Through the process of drug repurposing, promising candidate pharmaceuticals have been found, which may lead to the discovery of novel treatment approaches to combat existing viral infections and potentially developing viruses [12].

CURRENT ANTIVIRAL LANDSCAPE

Existing Challenges in Antiviral Therapy

In addition to endangering public health and creating a financial burden, viral infections have a high rate of morbidity and mortality [13]. The COVID-19 epidemic has impacted over twelve million individuals, which is the result of a novel SARS-CoV-2 disease that has killed over 55,200 people globally [14]. Although there are a number of unknown reasons, practical experience may reveal more restrictions on oral antivirals because of their unfavorable interactions with other medications [15]. The main outer glycoprotein coat of the virus, the CoV S-protein, is what essentially determines protective immunity. Variations in the S-protein of the previously discovered CoVs and the recently emerged ones, once they infect the human population, would significantly impede the creation of vaccines [16]. Furthermore, it is important to take into account possible causes of hepatitis, especially in immunocompetent children, as it is difficult to identify complex cytomegalovirus infections [17]. The most difficult task is quickly identifying therapeutic, developmental, and interventional technologies that are effective for the serious global public health concern connected with COVID-19 [18].

Limitations of Current Antiviral Therapies

The effectiveness rate of designing pharmaceuticals to combat viruses has declined in the last few decades, leading some analysts to claim that the sector is experiencing an innovation crisis. A decline in the total level of effectiveness of pharmacological agents is indicated by a spike in the average production period, a rise in the percentage of discontinuation for pharmaceuticals in development, and an increase in the expense per new medicine that is subsequently granted a license for use [19]. One important drawback of influenza treatment is the rise of drug-resistant influenza strains as a result of the existing antiviral medication regimens.

CHAPTER 3

In-silico and Target-based Approaches for Drug Repurposing in Antiviral Therapy

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Abstract: The ongoing challenges in antiviral drug development, exacerbated by the emergence of novel viruses and the need for rapid therapeutic solutions, have led to a growing interest in drug repurposing strategies. This chapter explores the dynamic landscape of drug repurposing in antiviral therapy, focusing on the synergistic integration of *in-silico* and target-based approaches. The chapter begins with an introduction to the significance of drug repurposing in overcoming traditional drug development hurdles. It delves into *in-silico* approaches, elucidating the role of computational methods, molecular docking, and bioinformatics tools in identifying potential repurposed drugs. Simultaneously, the chapter investigates target-based approaches, highlighting the importance of target identification, validation, and screening strategies. Emphasizing the transformative potential of integrating *in-silico* and target-based methods, the chapter explores how combined approaches enhance the efficiency and accuracy of drug repurposing. Challenges, such as ethical considerations, data quality, and regulatory hurdles, are addressed, providing a comprehensive overview of the field's complexities. Future perspectives, including the role of emerging technologies and personalized antiviral therapies, are discussed to guide further research. The chapter concludes with a detailed analysis of case studies, focusing on successful examples like Remdesivir and other notable instances, offering valuable insights and lessons for the future of antiviral drug repurposing. This comprehensive exploration contributes to the evolving landscape of drug development, providing a roadmap for researchers and clinicians engaged in the critical endeavour of combating viral infections through innovative and efficient therapeutic strategies.

Keywords: Antiviral therapy, Drug repurposing, *In-silico* approaches, Molecular docking, Target identification.

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INTRODUCTION

Antiviral drug development has been a perpetual challenge in the face of evolving viral threats, necessitating innovative approaches to expedite the discovery of effective treatments. Traditional drug development processes are encumbered by prolonged timelines [1], escalating costs, and the urgent need for rapid responses to emerging viral outbreaks. In this context, drug repurposing, the strategic repositioning of existing drugs for new therapeutic applications, emerges as a promising avenue to surmount these challenges [2]. Historically, the development of antiviral therapies has involved a painstaking journey, from the discovery of novel compounds in the laboratory to their eventual clinical use. This traditional approach, although invaluable, has proven to be time-consuming and economically burdensome, particularly in the face of swiftly mutating viruses [3]. As we navigate the complexities of antiviral drug development, there is a compelling need for alternative strategies that can offer expedited solutions while maintaining efficacy and safety standards. The significance of drug repurposing in the realm of antiviral therapy lies in its ability to circumvent the protracted timelines and resource-intensive processes associated with de novo drug development [4]. By exploring existing drugs with established safety profiles, drug repurposing offers a shortcut to clinical application, potentially mitigating the devastating impacts of viral outbreaks. This strategy aligns seamlessly with the urgency of responding to emerging viral threats, providing a practical and efficient means to identify and deploy effective antiviral treatments [5].

Moreover, drug repurposing holds promise as a sustainable approach, making optimal use of pharmaceutical investments already made in the development of approved drugs [6]. As we stand at the intersection of innovation and necessity, the value of drug repurposing becomes increasingly evident, representing a paradigm shift in antiviral drug development that embraces both speed and efficiency. The scope of this chapter is to delve into the dynamic landscape of drug repurposing for antiviral therapy, with a specific focus on the integration of in-silico and target-based approaches. Through a comprehensive exploration of computational methods, molecular docking, and bioinformatics tools, alongside the strategies involving target identification, validation, and screening, this chapter aims to unravel the synergies that can enhance the efficiency of drug repurposing [7]. By addressing challenges such as ethical considerations, data quality, and regulatory hurdles, the chapter aspires to provide a holistic understanding of the complexities involved in antiviral drug repurposing. Future perspectives, including emerging technologies and personalized antiviral therapies, will be discussed alongside case studies, offering valuable insights for researchers, clinicians, and policymakers navigating the ever-evolving landscape of antiviral drug development.

Background and Rationale

Traditional antiviral drug development requires years of research, development, and clinical trials to bring new compounds from the laboratory to clinical use [8]. This approach is costly and time-consuming, particularly when faced with rapidly mutating viruses such as influenza or emerging viruses like SARS-CoV-2 (Fig. **1**).

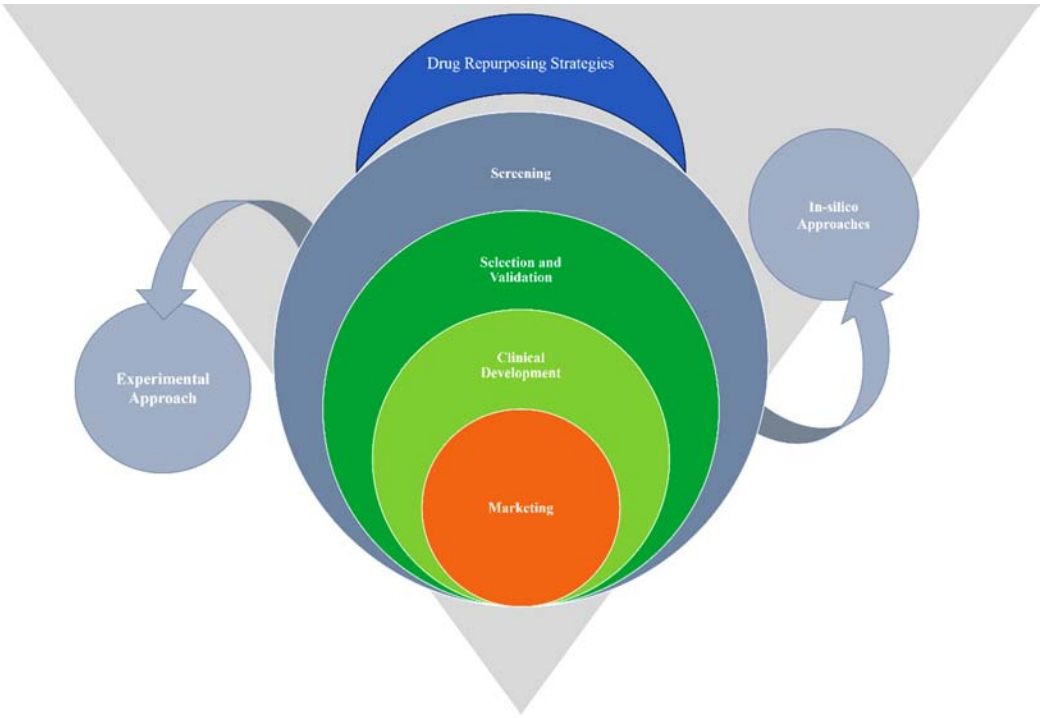

Fig. (1). Two alternative and complementary drug repurposing approaches: one is an experiment-based approach, and the other is a theoretical or in-silico-based approach.

Drug repurposing offers a strategic shortcut by identifying existing drugs with known safety profiles for new therapeutic applications. It can significantly reduce the time and costs associated with drug development because repurposed drugs have already been proven safe for human use [9]. Moreover, given the urgency of responding to emerging viral outbreaks, drug repurposing provides a means of quickly deploying effective treatments [10].

Significance of Drug Repurposing in Antiviral Therapy

The significance of drug repurposing in antiviral therapy lies in its ability to utilize existing drugs with known pharmacological and toxicological profiles, thus speeding up the availability of treatments [11]. For instance, remdesivir, originally

CHAPTER 4

In-vitro Methods for Drug Repurposing in Anti-Viral Therapy

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Abstract: Emerging viral and re-emerging epidemic viral infectious diseases continued by global commerce, travel, and ecological system alteration are of public health concern. Despite concerted efforts and successful vaccination in limiting viral infections, humans are still terribly losing the battle against the microbes. Persisting pandemics, acquisition of drug resistance, and emerging and re-emerging microbes impose challenges and add substantial time and costs to develop broad-spectrum antivirals, which ultimately leads to prolonged hospital stays and doctor visits and increases global mortality. In this regard, drug repurposing is a great way to find new applications for already-approved therapies that circumvent numerous time-consuming experiments as well as financial costs associated with novel drug development. Screening of drugs directly using animals or *via in-vivo* method is challenging, time-consuming, and expensive, which limits the assessment and re-use of already available drugs for repurposing. *In-vitro* drug testing is a vital stage in the drug discovery process and also reduces animal usage. To date, several *in-vitro* approaches are in use for the screening of new anti-viral agents and already approved strategies for drug repurposing. *In-vitro* anti-viral testing of compounds or any available market drug can assess the potential effectiveness in the pre-clinical model of anti-infective and deliver imperative information to determine the best combination ratios and dosing schedule. This chapter summarizes different traditional as well as modern *in-vitro* (biochemical and cell-based a) methods viz. TCID50, EC50 /CC50, Plaque, HAI assays (hemagglutination inhibition), ELISA/Luminex, Plaque-Reduction Neutralization Tests (PRNTs), plaque assays, or RT-PCR analysis, cytopathic effect (CPE)-based drug screening, and a high-throughput, high-content Automated Plaque Reduction (APR) used for the repurposing of drugs as anti-viral agents. Additionally, the chapter will provide the shortcomings, advantages and challenges of these modern and traditional methods. Information regarding the plant extracts, their active constituents, available

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marketed drugs, and compounds from different sources, which were remedies for different pathologies and were repurposed as anti-virals by using these methods, is also compiled.

Keywords: Antivirals, Cell-based assays, Cell-based techniques, Preclinical evaluation, Viral diseases.

INTRODUCTION

Virus-related infectious diseases are the leading cause of morbidity and mortality worldwide, with developing nations being the most affected by these infections. There are currently more than 200 virus species that are known to infect humans. Every year, on average, three to four new or re-emerging viruses are identified, and over half of them have an animal origin and/or are directly transmitted by animals [1]. The animal world is the source of 60% of the agents recognized by the World Health Organization (WHO) as human infections. Seventy-five percent of newly discovered human viruses during the last three decades have the ability to traverse the animal-human interface [2]. Additionally, the excess use of antibiotics affects global public health severely and continues to be threatening by virtue of antibiotic resistance. There are still major risks to human beings from viral pandemics like COVID-19 [3]. Prominent viruses like hepatitis B and HIV-1 affect millions of individuals worldwide each year. Pharmaceutical corporations and university research centers have been working progressively harder in the past few years to develop safe and effective medications to treat viral disorders [4]. Novel, more potent, and selective derivatives of existing drugs have been produced, and new classes of antiviral agents have been identified. The screening of synthetic as well as natural products from different sources, microorganisms, plants, algae, *etc*., is still expected to provide results, and several new active compounds are being reported [5, 6]. Despite the new advances in managing certain viral diseases, targeted treatment for the majority of viral infections remains insufficient. Indeed, the demand for effective therapeutic techniques to combat “old,” emerging, and re-emerging viruses is greater than approved antivirals. Testing a large number of molecules in a short amount of time is a major obstacle in the process of screening antiviral drugs derived from different sources [7]. Traditional drug discovery compromises different stages to get the marketing approval for the newly discovered drug. Traditional drug discovery and development involves several stages for the discovery of a new drug and to obtain marketing approval. Approval of a novel medicine is a costly process that takes ten to fifteen years. Because of this drawn-out discovery process, medication repurposing, or repositioning, is now an option for reducing the amount of time and cost needed to develop a drug [8]. Drug repurposing, also known as drug repositioning or drug reprofiling, is a strategy that finds new clinical uses for

authorized or experimental medications outside of their original intended usage. This strategy typically emerges from the coincidental finding of unintended consequences or recently identified functions of already-approved medications. Recent years have seen a lot of coverage of drug repositioning or repurposing in the scientific literature, which has led to the creation of new intellectual property and Investigational New Drug (IND) filings. This approach can be a much faster and cheaper way to develop new treatments for viral diseases than traditional drug discovery methods. The literature shows a clear tendency toward the generation of first repositioning hypotheses by computational or informatics-based methods, followed by targeted evaluation of biological function through phenotypic experiments. Using *in-vitro* screening to find and evaluate candidates for repositioning of established medications or drug-like compounds in disease-relevant phenotypic assays is another feasible approach for drug repositioning. This method can focus on subsets of recognized medications or molecules resembling drugs or use huge compound libraries. *In-vitro,* which means "in glass," refers to experiments conducted in a controlled environment outside of a living organism. In drug repurposing, this involves using cells or cellular components to identify existing drugs that may be effective for new therapeutic applications [9].

Many medications, such as chlorcyclizine, manidipine, favipiravir, nitazoxanide, lopinavir/ritonavir remdesivir, molnupiravir, nirmatrelvir/ritonavir (Paxlovid™) that were examined and approved previously were repurposed as antivirals have been approved or authorized for use in emergencies. In addition to these, many drugs are under clinical trials for their use against non-approved clinical conditions [10]. To date, several types of *in-vitro* cell-based assays and other techniques are already used for the development of new strategies from the existing drug. These methods are cell-based assays such as cell proliferation and techniques such as immunofluorescence, ELISA, RT-qPCR, immunoblotting, viral plaque assay, flow cytometry, viral replication kinetics, viral Titer by TCID50 (Median Tissue Culture Infectious Dose) assay, dot blot, automated cell-based luminescence, co-immunoprecipitation, phospholipid accumulation test, pseudo-virus-based assays to measure antibody-mediated neutralization, automated image-based assay, cell-to-cell fusion inhibition, high-Throughput antiviral testing using image cytometer, cytopathic effect (CPE)-based drug screening assays and multiplexed multicolor antiviral assay [11 - 20]. In this chapter, we explore the different *in-vitro* methods used for drug repurposing of antivirals against a range of emerging or re-emerging infections, their advantages, challenges, and different drugs assessed for repurposing against viral disorders.

CHAPTER 5

In-vivo Methods for Drug Repurposing in Antiviral Therapy

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Abstract: *In-vivo* models or animal-based evaluation of any new chemical/ natural entity is a necessary stage of the drug development process. To validate the realistic efficacy of an *in-vitro* lead for clinical use, pre-clinical animal models are widely used and also form regulatory requirements in the licensing process, as *in-vitro* experiments only provide a potential extracellular drug concentration. However, thorough investigations using *in-vivo* models give more details regarding free as well as unbound drug concentrations present in interstitial fluid. Translation of already approved drugs for new and emerging viral diseases through repurposing can be a time-reducing, cost-effective, and sustainable process as compared to finding a new drug. Considering the complex interaction of infective agents with the host immune and neuroendocrine system, the selection of an appropriate animal model is crucial for getting the pertinent, and precise translatable data. For drugs that have already been approved by the FDA, *in-vivo* drug dose and exposure period along with pharmacokinetics data, are generally known for a disease. This an be utilized to assess a drug's potential usefulness in treating novel viral indications. Despite of this, anti-infective animal models are primarily limited to the screening of anti-viral monotherapy and are not substantially employed for combinational chemotherapies. Here, this chapter summarizes the different animal and *in-vivo* models that are in use for screening as well as the repurposing of drugs for their anti-viral efficacy against numerous emerging and re-emerging fatal viral diseases.

Furthermore, the chapter will also provide information regarding the pros and cons of different in-use *in-vivo* models for various viral infections, including diseases of global public health concern.

Keywords: Animal model, Antiviral, Drug repurposing, Viral diseases, Vaccines.

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INTRODUCTION

Infectious diseases continue to be the foremost reason for human and animal fatality and remain a crucial global challenge, leading to substantial healthcare expenses. In spite of an elaborate armamentarium to combat microbes and major pandemics like AIDS, it is still challenging to fight against new infectious diseases. Mortality and morbidity associated with viral infections, including HIV and COVID-19, continue to present major concerns [1]. The development of new drugs for emerging and remerging viral infections is a time-consuming process. In this context, the repositioning of drugs has always attracted a lot of attention because of the several advantages linked with drug re-profiling, such as decreased failure rates and lessened time vis-à-vis resource consumption [2, 3]. Drug repurposing, also known as drug repositioning, is a process of identifying new therapeutic uses for existing FDA-approved clinically used drug molecules drugs [4]. This therapeutic switching strategy offers a faster and more cost-effective approach to drug development compared to traditional methods of discovering entirely new drugs. A medicine that has been repurposed may also have a new formulation, dosage, mode of administration, or patient base. There are different terms used for drug repurposing, *viz*. drug re-profiling, re-tasking, rescue, indication expansion, or switching [5]. *In-vivo* methods for drug repurposing in antiviral therapy leverage living organisms, typically small animals, to assess the efficacy and safety of existing drugs for treating viral infections. Compared to *in-vitro* (cell-based) methods, *in-vivo* studies provide a holistic picture of a drug's potential as an antiviral treatment by taking into account factors like Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) within an organism [6, 7]. Human-based models are useful tools at all stages of drug development, from high-throughput screens to find target or lead molecules to preclinical efficacy and safety testing, as well as clinical trial execution and decision-making [8]. Preclinical models are a necessary step in identifying a drug candidate that shows auspicious effects before proceeding to phase II clinical trials. Although vaccines and small-molecule antiviral medicines are available, many viruses still lack effective non-toxic prevention and treatment approaches. Using monoclonal and polyclonal antibodies along with the repurposing of available drugs in antiviral treatments could bridge the gap and offer effective virus-specific medical interventions [9]. Preclinical animal models play the utmost critical importance in the developing and re-profiling of any therapeutic antibodies or drugs. Due to differences in pathogenesis, immunology, and general features, the ideal animal model for human viral infection varies between each virus species. Therefore, certain key points should be considered at the time of selection and development of representative experimental animal models [10]. First, the disease course in an animal model should ideally mimic and replicate the interactions between the host and pathogen, clinical outcome, and immunological characteristics as they occur

naturally during human viral infection. Secondly, the vulnerability of species to infection should be assessed. Furthermore, for a better understanding of pathology, clinicopathological and immunological parameters of the disease process, viral replication should be accompanied by noticeable clinical symptoms and anomalies, as observed in human viral infections. Researchers developed multiple different types of animal models that closely depict human disease for a specific pathogen. Amongst different types of animal models, small animal models are most appropriate for initial screening and assessing vaccination or treatment efficacy. However, nonhuman primate (NHP) models are often employed for important preclinical investigations [9]. To date, different types of *in-vivo* models are established and categorized into different sub-groups. Although *in-vivo* models have several advantages and are a bridge between the *in-vivo* and clinical phase, this method of drug evaluation is associated with several disadvantages and shortcomings. This chapter will summarize different types of animal models or *in-vivo* methods used for the screening of a drug as repurposing for viral infections, along with their advantages and disadvantages.

TYPES OF VIRAL DISEASE AND IN-USE DRUGS

Viral diseases can range from minor infections to catastrophic pandemics. Due to the immense dissimilarity in viruses in terms of epidemiology and pathophysiology, there is no one-size-fits-all control strategy [11]. Viral infections are a common cause of illnesses among people of all ages. Generally, the extent of illnesses is wide; nevertheless, young children and people with diminished or inadequate immune systems are at the most risk of developing serious diseases [12]. Viruses are unicellular creatures enveloped by a protein coat containing DNA or RNA as genetic material. Infectious viral diseases emerge when a pathogenic virus infects and proliferates inside a host organism and overcomes its immune mechanism. To date, several categories of viral infections have been reported, and they are sub-grouped either on the basis of the site of infection, types of viruses, or mode of transmission. These diseases possess varied symptoms and are often contagious. Additionally, symptoms of viral infections also rely on the virus type instigating the infection, the organs infected, the age of the afflicted individual, and additional risk factors. Some common types of viral infections are available in used drugs depicted in Fig. (**1**) and Table **1**.

CHAPTER 6

Applications of AI/ML in Drug Repurposing for Antiviral Therapy

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Abstract: Recent advancements in artificial intelligence have made strides in all aspects of human life. The drug development process has enhanced significantly, especially during the COVID-19 period. AI has made the *in-silico* methods even faster and more accurate, which are now more capable of guiding the initial stages of drug discovery. AI-based protein structure prediction has made it possible to avail the dynamic structure 3D of proteins, which is not possible through crystallography or other wet lab techniques. Advanced AI algorithms are being developed to cater to the specific characteristics of ligands, proteins, and different steps of drug development. With time, more relevant data are becoming available, which will improve AI-based experiments even further. This chapter has enlisted computational methods used with AI and how they differ from the traditional physics-based approaches. Under this framework, the chapter aims to gain insight into the primary research on drug repurposing for application in the treatment of viral infection using AI and ML techniques. Suramin, a polyanionic sulfonate antiparasitic drug, showed potential antiviral activities in the Zika virus (ZIKV) infection. Likewise, Sofosbuvir, a viral protease inhibitor primarily used for anti-hepatitis C virus infection, can be reused as a prophylactic treatment in SARS-CoV-2.

Keywords: Computational Chemistry, De Novo Protein Design, De Novo Drug Discovery, Deep Learning, Generative AI, Machine Learning, Machine Learning Force Fields, SARS-CoV-2., Virtual Screening, Zika Virus.

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INTRODUCTION

In the process of drug discovery, two initial steps are fundamental; one is the identification of the bioactive ligand or small molecules, which are also known as chemical substances. The second important step is the identification of the target protein structures or macromolecules. The 3D structure of both the biomolecule and the chemical molecule is important as it conveys important information about the characteristics and properties of the substance in question. To date, only about 9000+ drugs have been approved by the FDA, and experimentally known protein structures are very few, only about 24,000, and among them, only 6,200 proteins are of human origin. There is a large gap between the available amino acid sequence and available three-dimensional protein structures, which are necessary for drug development and repurposing [1].

DIFFERENT COMPUTATIONAL METHODS

All of the computational methods used in drug discovery are based on three approaches. Although they differ from each other in their basic principle and based on the computational cost, accuracy, and required time; Ab initio, Semiempirical, and Empirical are the three methods that are fundamental in computational methods.

Ab initio is a Latin term that means “from the beginning.” The Ab initio methods are based on the first principles (theoretical principles) and do not depend upon any experimental data. The Ab initio approach is used to solve the Schrodinger equation of a given molecular system, as it takes into account all the interactions between all the atoms and electrons. These methods of calculation are very time-consuming and computationally expensive. They do not require any experimental data, based solely on theory, taking physical constants as the input. Empirical methods use experimental data, which are known, this data is used to predict the internal electronic energy of the system. They describe energy as a function of geometrical parameters like bond lengths, bond angles, *etc*. Force fields are used to describe the entirety of the system. These systems have parameters that fit experimental values for specific molecules and atoms. Semiempirical methods are a hybrid approach of the ab initio and empirical methods. They can be used in large biological systems as the computational cost is much less than the ab initio methods [2 - 4].

MACHINE LEARNING (ML) MODELS

The very idea of machine learning is to find patterns in our existing data and make new predictions. The entire observable physical world around us can be interpreted as a form of data. While working on drug discovery, we rely on

empirical data to make decisions. Machine learning models use this data and, with the help of different mathematical functions, make a model that can make predictions when new data is fed into it [5].

ML is a part of AI that can be further divided into three parts: Supervised Learning, Unsupervised Learning, and Reinforcement Learning. Supervised data is labeled and used as the input data and a model is built with that data through training. The training follows different algorithms for different models. Then, the trained model is applied to new test data, which is also labeled. Then new prediction is made for the test data set, and then several validation matrices are calculated [6].

MACHINE LEARNING APPROACHES *VS.* CLASSICAL COMPUTATIONAL METHODS

Classical computational methods focus on either classical (Newtonian and Hamiltonian) physics or quantum mechanical approaches or, in some cases, a hybrid mixture of both. For example QM/MM energy calculation of biological systems. However, in recent times, machine learning-based approaches have emerged, which are replacing the time-consuming ab initio methods. Machine learning models can also be physics-aware to harness the robustness of physics-based approaches [7].

Feature-based machine learning can be further classified as Supervised, unsupervised, and self-supervised. Supervised learning contains labeled data, which is the input data that is already classified or categorized. The model is trained to map the relationship between the labels and the input features or descriptors. Some of the most popular and useful ML models that are used in AI-based drug discovery and drug repurposing are described [8].

Naive Bayesian (NB)

It is a probabilistic classifier that describes a probability based on prior knowledge. The 'naïve' aspect assumes that all the features are independent of each other within each class. It is a supervised classification-based algorithm that calculates the probability of new unlabeled data belonging to each class. NB is used extensively in QSAR and ADMET studies. It has also been used in drug-target interaction prediction as well [9].

Support Vector Machine (SVM)

SVM is a supervised machine learning model used in classification and regression. SVM creates a hyperplane that divides the data points of different

CHAPTER 7

Nano-Formulations of Repurposed Drugs for Antiviral Therapy

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Abstract: New viruses are always emerging, endangering global health systems. Uncontrolled epidemics have the potential to develop into pandemics that severely impact our healthcare and financial infrastructures as we have faced COVID-19. Viral illnesses kill millions of people worldwide each year. There are several limitations and problems with the antiviral treatment that need to be fixed right away. These include resistance situations, increased dosage and frequency of administration, bioavailability problems, non-specificity, *etc.* The advancement of nanomedicine could aid in overcoming these challenges. To reduce the previously described adverse effects of antiviral treatment, current research emphasizes the need for a greater understanding of the potential and precise application of diverse lipid, polymer, nanoparticles, and elemental-based nanoformulations. Since there is presently no globally approved treatment for viral infection, which contributes to the rapid spread of viruses and the growing need for prompt action, drug repurposing has emerged as one of the primary strategies in the battle against viral infection. Repurposed drugs are currently being tried against viral infection to control hyper-inflammation and an overreaction to the immune system in cases of severe sickness or to address the replication and spread of the virus. Nanotechnology may be able to address several issues with traditional antiviral therapies. For example, the pharmacokinetic profile of antiviral drugs can be greatly enhanced while reducing their systemic toxicity by employing nano-delivery vehicles. Another unique nanomaterial's virucidal or virus-neutralizing properties may be put to use.

Keywords: Drug repositioning, Nanomedicine, Nano drug delivery, Virucidal formulations.

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INTRODUCTION

The effectiveness of antiviral medications may be diminished by resistant virus strains, and extended use of antiviral treatments may result in unfavourable side effects. Consequently, viral infections pose a significant threat to worldwide health. In recent years, there has been a great deal of interest in and use of a novel approach to using nanotechnology in medicine (*i.e.*, nanotherapeutics and nano delivery systems) to increase the effectiveness of bioactive molecules in a variety of medical domains, including drug development and fundamental research [1]. Treatment for viral infections has considerably improved thanks to nanomedicines [2]. Viruses are a constant danger to people, plants, and animals. Although humans can contract hundreds of viruses and become unwell as a result, most of them are incurable. Concerned about viruses that are developing or reappear are public health officials [3]. The viruses that cause West Nile, yellow fever, Rift Valley fever, dengue, Ebola, SARS, MERS-CoV, zika, Crimean Congo hemorrhagic fever, severe fever with thrombocytopenia syndrome, chikungunya, and influenza A are among these pathogens. Global travel and migration, trade, technology, industry globalization, agricultural growth, and climate change are all contributing to the introduction and reemergence of viruses that can spread quickly and spark a pandemic [4].

A prime illustration of how a newly discovered virus could spread and start a pandemic is the emergence of the human immunodeficiency virus in the 1980s [5]. Antiretroviral drugs can be used to treat human immunodeficiency virus, but there is no known cure [6]. To treat influenza viruses, there are vaccinations and antiviral medications available. However, antiviral resistance emerges as a result of the ongoing evolution of these viruses [7]. Targeting strategies for antiviral drugs at different phases of the viral life cycle are shown in Fig. (**1**). The 2013 human influenza outbreaks in China raised serious concerns due to the new avian influenza virus's potential for worldwide spread [8]. Experts believe there's a possibility the virus will spread among individuals and cause an international pandemic [9]. These conditions all call for the creation of novel, potent, broad-spectrum antivirals. When it comes to treating certain viruses, such as hepatitis C or the human immunodeficiency virus, the conventional one virus, one medicine method has proven to be incredibly effective. The main goal of this approach is to create substances that specifically target viral proteins [10]. Most authorized antiviral drugs are very virus-specific since their main target is a viral protein. However, there are certain disadvantages to direct-acting antivirals. A potential method that might lead to a quicker and less costly approval process for novel therapies for viral infections is drug repurposing or repositioning [11]. Drug repositioning is superior to traditional drug development because the drug being moved has already undergone multiple studies that have established its safety and

decreased the risk of failure. While relocated medications may be able to avoid phase I clinical research, phase II and III trials are still necessary to determine their effectiveness for the new ailment [12]. The patents on various drugs have occasionally been revoked, just like with generic drugs. Periodically, patents for second medical uses may be granted to medications with unique formulations or therapeutic uses. To aid in the repurposing of these medications, however, is to increase the number of academic centres' researchers and practising physicians who participate in clinical trials.

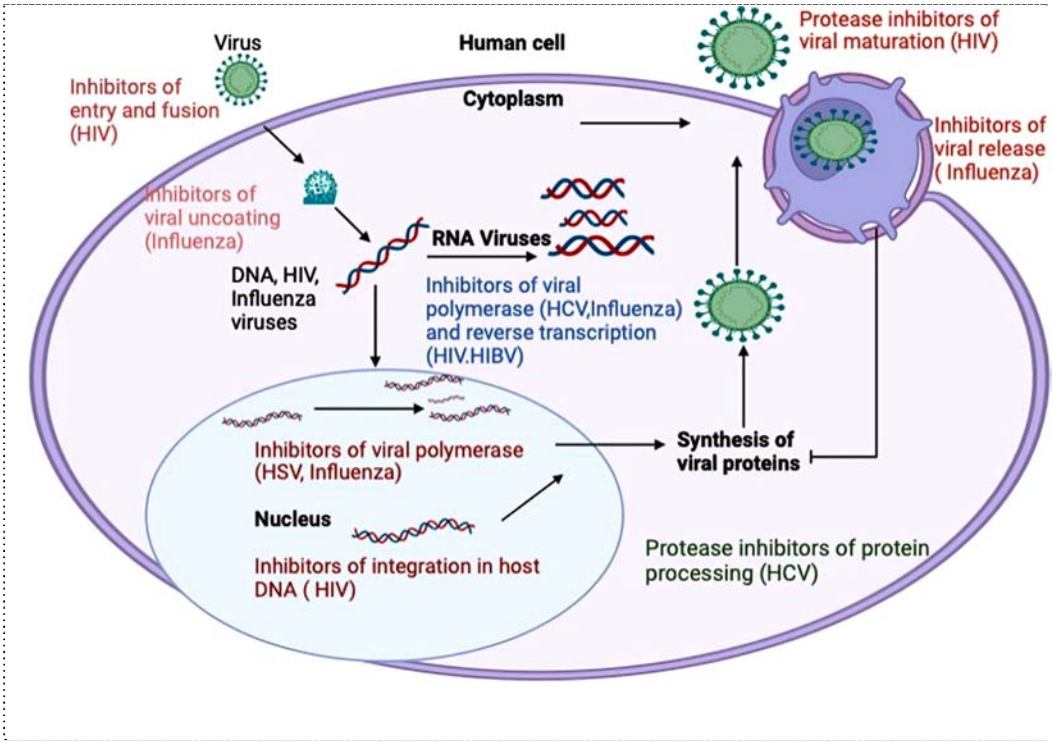

Fig. (1). Targeting strategies for antiviral drugs at different phases of the viral life cycle.

HIV/AIDS treatment and monitoring could be drastically altered by the cutting-edge, multidisciplinary science of nanotechnology [13, 14]. The use of nanoparticles in the treatment of HIV infection may offer benefits such as sustained drug release, drug penetration into safe havens, and the ability to combine, encapsulate, or integrate multiple medications to target different cell types. Nanotechnology may be used to deliver antiretroviral medications to the central nervous system reservoir, minimizing the harm caused by infection and halting the virus' spread [15].

CHAPTER 8

Pharmacoeconomics of Repurposed Drugs for Antiviral Therapy

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Abstract: Emerging or re-emerging viruses are still major threats to public health. Prophylactic vaccines represent the most effective way to prevent viral infections. However, antiviral therapies are more promising for those viruses against which vaccines are not effective enough or contemporarily unavailable. The emergence of repurposed drugs for antiviral therapy has gained significant attention in recent years due to their potential to offer cost-effective solutions amidst the ongoing challenges posed by emerging and re-emerging viral infections. This book chapter provides a comprehensive analysis of the pharmacoeconomics surrounding the repurposing of drugs for antiviral therapy. It examines the economic implications of repurposed drugs compared to traditional drug development approaches, considering factors including development costs, time-to-market, regulatory pathways, cost-effectiveness, *etc*. Furthermore, the chapter explores the impact of repurposed antiviral drugs on healthcare systems, highlighting their potential to mitigate the economic burden associated with viral outbreaks. Finally, we discuss potential avenues for further investigation in drug repurposing efforts.

Keywords: Antiviral therapies, Clinical efficacy, Clinical trials, Comprehensive analysis, Cost-effectiveness, Drug development, Drug discovery, Drug effectiveness, Drug repurposing, Economic burden, Viral infections.

INTRODUCTION

Viral diseases consist of a diverse array of infections caused by a multitude of viruses, each with its unique characteristics and modes of transmission [1]. Viruses themselves are intricate structures, ranging from 20 to 300 nanometers in size, and exist in various morphological forms [2]. They are composed of either single or double-stranded DNA or RNA enclosed within a protein, glycoprotein,

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or lipid coat. Additionally, they lack the machinery for independent metabolism and replication. Instead, they rely on the cellular machinery of host organisms to proliferate [3]. Upon entering a host cell, viruses release their genetic material, which then integrates into the host cell's genome, effectively stealing its cellular machinery. This process enables the virus to replicate and propagate, often leading to the destruction of the host cell. Of note, infected cells may undergo uncontrolled proliferation, further amplifying viral spread within the host organism [4]. The immune system of the host organism mounts a defense against viral infections, producing specific antibodies to neutralize the virus and infected cells [5]. However, the rapid evolution and dissemination of viruses pose significant challenges to manage these infections. The control and prevention of viral infections have long relied on traditional epidemiological measures including case isolation, contact quarantine, and mass vaccination, given the limited availability of specific antiviral treatments [6]. Unfortunately, the existing antiviral therapies remain unsatisfactory due to several factors, leading to their ineffectiveness in certain cases. The factors include the rapid mutation rate of viruses (RNA viruses like HIV and influenza), leading to drug resistance [7, 8]. Additionally, the complexity of viral infections poses challenges in designing effective antiviral drugs. Viruses often establish latent infections or reservoirs within the body, evading the immune system and standard antiviral treatments. This complexity requires multifaceted approaches, including combination therapies and immune modulation, to achieve successful viral suppression. This calls for the development of new antiviral therapeutic approaches that are cost-effective and exert negligible side effects. For this reason, the emergence of repurposed drugs has gained significant attention in the field of antiviral therapy.

Repurposed drugs, also known as drug repositioning or drug rediscovery (Fig. **1**), involve identifying existing drugs approved for other indications and investigating their efficacy against viral infections [9]. The advantage of repurposed drugs lies in their established safety profiles and pharmacokinetic properties, which accelerate the drug development process [10]. By utilizing existing drugs, researchers can bypass many stages of preclinical and early clinical trials, potentially bringing effective antiviral therapies to market more rapidly [11]. Furthermore, it offers a cost-effective solution compared to de novo drug discovery. Developing a new antiviral drug from scratch involves substantial time, resources, and financial investment [12]. In contrast, drug repurposing already has established manufacturing processes and regulatory approval, reducing the overall cost and time required for development [13]. Moreover, this provides an opportunity to explore alternative mechanisms of action against viral infections. Drugs approved for unrelated indications may exhibit unexpected antiviral activity, offering novel treatment avenues for viral diseases [14]. However, this approach also exhibits certain challenges, including identifying

suitable candidates and understanding their mechanisms of action against specific viruses. Also, they may not always exhibit potent antiviral activity or may have limited efficacy against certain viral strains [15]. Despite these challenges, the emergence of repurposed drugs represents a promising strategy in the management of viral infections. Table **1** shows all the potential drug candidates repurposed for viral infections. Evaluating the cost-effectiveness of new antiviral therapies, including repurposed drugs, is important. Therefore, pharmacoeconomics plays a key role in assessing the economic impact of different treatment options, including their costs and benefits. This analysis considers not only the direct costs of antiviral drugs but also indirect costs such as hospitalization, productivity losses, and long-term care associated with viral infections [16]. By comparing the costs and outcomes of various treatment strategies, pharmacoeconomic analysis helps identify the most efficient allocation of resources to maximize health outcomes within budget constraints [17]. Moreover, pharmacoeconomic analysis informs healthcare policies and reimbursement decisions. Governments, insurers, and healthcare providers rely on economic evaluations to determine which antiviral therapies should be included in formularies or reimbursed by insurance plans [18]. By incorporating cost-effectiveness data, policymakers can ensure equitable access to effective antiviral treatments while optimizing healthcare spending. Additionally, pharmacoeconomic analysis guides research and development priorities in the pharmaceutical industry [19]. Drug manufacturers use economic evaluations to prioritize investment in antiviral drug development based on potential market demand and expected return on investment [20]. This process incentivizes the development of cost-effective antiviral therapies, including repurposed drugs, that address unmet medical needs and offer value to patients and healthcare systems. Furthermore, pharmacoeconomic analysis facilitates informed decision-making by healthcare providers and patients. Clinicians consider cost-effectiveness data when selecting antiviral treatments, weighing the clinical benefits against the economic costs for individual patients. Patients, meanwhile, may factor in out-o--pocket expenses and insurance coverage when making treatment decisions, guided by the economic value of different therapy options [21]. This chapter deals with the significance of pharmacoeconomics in assessing the economic viability of new antiviral therapies, including repurposed drugs, and its implications for healthcare stakeholders, patients, and the pharmaceutical industry.

CHAPTER 9

Clinical Trial of Repurposed Drugs for Antiviral Therapy

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Abstract: Recent times have witnessed an urgent need for effective antiviral therapies, especially after the COVID-19 pandemic. Traditional drug discovery processes are often time-consuming and resource-intensive, prompting the exploration of alternative approaches like drug repurposing. This chapter aims to provide insights into the potential of drug repurposing as a viable strategy for combating viral infections and improving public health outcomes. Drug repurposing involves investigating existing drugs, already approved for one indication, for their therapeutic potential against other diseases, including viral infections. This approach offers several advantages, such as reduced cost and time for clinical application, as repurposed drugs have already undergone rigorous safety and pharmacokinetic evaluations. Zidovudine, molnupiravir, and remdesivir are some of the examples of the successful repurposed drugs that have demonstrated efficacy against various viral infections. However, there are instances where repurposed drugs have not shown significant therapeutic benefit, as in the case of hydroxychloroquine for managing COVID-19. Recent technological advancements, such as artificial intelligence and computational biology, could revolutionize drug repurposing for antiviral therapies. However, identifying potential drug candidates for repurposed antiviral therapy, its safety, efficacy, and clinical outcome remains a challenge.

Keywords: Antiviral, COVID-19, Drug repurposing, Drug discovery, Pharmacokinetics, Safety.

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INTRODUCTION

The world is witnessing an ongoing battle against viral infections. Considering the recent emergence of the COVID-19 pandemic, the quest for effective antiviral therapies remains a critical endeavor [1]. Traditional approaches to drug discovery are highly time-consuming, tedious, and resource-intensive process, which often takes more than 15 years for one potential drug candidate to find clinical application [2]. Technological advancement in recent times and the emergence of high throughput screening methods have boosted the process of drug discovery, in which repurposed drugs have emerged as a promising avenue. Repurposing a drug involves investigating existing drugs, which are in clinical application for one indication, for their therapeutic potential against other diseases, which can include infections induced by viruses [3]. Accumulated evidence suggests that repurposing a drug offers several distinct advantages when compared to traditional methods of drug development by significantly reducing the time and cost for the clinical application of a new drug for a particular ailment [4]. Since repurposed drugs have already undergone rigorous investigation for pharmacokinetics, toxicity, and safety in humans during preclinical and clinical testing, this significantly reduces the time and resources required for regulatory approval and clinical application of the drug [4]. This concept is particularly important during viral outbreaks like COVID-19 witnessed recently, where rapid deployment of effective therapies is paramount to mitigate morbidity and mortality. Further, the concept of repurposed drugs adds to the existing scientific knowledge of the pharmacokinetics, mechanisms of action, and safety profile of existing drugs [4]. This knowledge base not only provides a solid foundation for rational drug selection and optimization but also enhances the likelihood of successful clinical outcomes. By repurposing existing drugs, researchers can capitalize on years of research and development efforts, potentially unlocking new therapeutic applications with minimal additional investment.

The multifaceted nature of viral infections, characterized by diverse host-pathogen interactions, presents a unique opportunity for drug repurposing [3]. Unlike antibiotics that directly target bacteria, antiviral drugs can inhibit viral replication or modulate host immune responses [1]. This versatility allows repurposed drugs to exert antiviral effects through various mechanisms, including disruption of viral replication machinery, inhibition of viral entry or fusion, modulation of host cell signaling pathways, and enhancement of immune responses [1, 3]. A recent example of successful drug repurposing is the use of nucleoside analogs like ribavirin and remdesivir, which were originally developed for treating infections induced by other viruses [5]. These drugs mimic natural nucleosides thereby disrupting viral RNA synthesis by inhibiting polymerase activity, resulting in halting viral replication. Ribavirin is used for Respiratory Syncytial Virus (RSV)

and hepatitis C infections, while remdesivir emerged as a potential drug candidate for managing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during the COVID-19 pandemic [6]. The ability to bypass the lengthy drug development pipeline makes repurposing particularly valuable in the context of emerging viral outbreaks and pandemics [3]. The repurposed drug can be rapidly evaluated in clinical trials to assess safety and efficacy against viral infections [1].

Despite its advantages, drug repurposing for antiviral therapy faces challenges, which include identifying suitable drug candidates that could demonstrable antiviral activity, elucidating their mechanisms of action, optimizing dosing regimens considering efficacy and safety, and mitigating potential adverse effects. Furthermore, successful repurposing necessitates a comprehensive understanding of viral pathogenesis, host immune responses, and drug pharmacology to guide rational drug selection and combination therapies. In this chapter, we aim to provide insights into the potential of drug repurposing as a viable strategy for combating viral infections and improving public health outcomes.

REPURPOSING DRUGS

Drug repurposing is a valuable strategy for targeting various infectious diseases. It highlights the various challenges that have been faced during the traditional drug discovery process, such as time consumption and cost constraints, and addresses the importance of identifying new drugs and targets [7]. It is a promising approach to accelerate the process of drug discovery for various infectious diseases and is very helpful in finding new effective drug candidates for various viral infections like influenza, HIV, hepatitis C virus, dengue, Ebola virus (EBAR), and many other life-threatening diseases [8]. There are two main strategies employed for pursuing drug repurposing: target similarity and target divergence [9]. Target similarity refers to a molecule that has been found effective against other viruses, so based on target similarities and common pathways that molecule can be hypothesized and tested for other viruses also. Likewise, in the target divergence approach, if the molecule's antiviral activity is not reported, it can be tested for the same target to explore the potential effect of the drug candidate against the various aspects of viral infection [9]. There are several potential drugs that have been repurposed for various emerging viral infections. Some examples of repurposed drugs include itraconazole, which was originally used as an antifungal agent and has been repurposed for prostate cancer and is currently undergoing Phase II trials for prostate cancer [10]. Similarly, metformin is an established antidiabetic drug for type II diabetes mellitus and is being repurposed for the therapeutic of prostate cancer [11]. Further, sildenafil was initially approved for the management of hypertension and is now in clinical application for treating erectile dysfunction and angina pectoris through

CHAPTER 10

Pitfalls of Drug Repurposing and Lesson Learned from COVID-19

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Abstract: The new beta coronavirus responsible for the current COVID19 pandemic had started to spread among people towards the end of 2019. Unmatched global searches were conducted to identify and reuse antiviral drugs from lists of approved drugs and recognised bioactive compounds. Antiviral drug development standards were rapidly circumvented, which often led to unsatisfactory results. The main drawbacks of this technique include promiscuous or cytotoxic compounds resulting in false positives. Several articles, press announcements, and media posts misled readers and occasionally diverted important attention from the search for reusable drugs. Funding for clinical trials with a low possibility of success, the empirical identification of factors that mitigate clinical indicators—such as the development of better disease management through immunomodulators and promiscuous/cytotoxic substances that cause inaccurate results—has led to breakthroughs in the clinic instead of in the lab.

Keywords: Baricitinib, COVID-19, Dexamethasone, Molnupiravir, Remdesivir, SARS-CoV-2, Tocilizumab.

INTRODUCTION

The world has experienced the worst health crisis after the 1918 influenza outbreak in the form of the coronavirus disease 2019 (COVID-19) pandemic, which has damaged people's health and economies everywhere [1]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causal agent of COVID-19. It is a unique strain of beta coronavirus group 2b, characterised by a single-stranded 5'-capped positive-sense RNA virus [2 - 4]. With a size ranging from 26 to 32 kb, the viral genome comprises 14 Open Reading Frames (ORFs) [2, 3] that can encode structural and nonstructural proteins in addition to a number of accessory proteins (Fig. **1**). The spike (S) glycoprotein, which is necessary for

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viral attachment and entrance, the Membrane (M), and Envelope (E) proteins, which are primarily needed for viral assembly and viral envelope development, are among the structural proteins. A helical nucleocapsid enclosing the viral DNA is another necessary component [5, 6]. Important enzymes required for viral replication, such as RNA-dependent RNA polymerase (RdRp) and viral proteases, are among the nonstructural proteins. The main body of the paper goes into additional depth about these enzymes because of their unique significance as druggable targets. The S-glycoprotein, which has also been well studied as the primary target of antibodies generated by both natural infection and immunisation, is another possible therapeutic target. This is true for every major vaccination platform that has shown to be the most effective to date, including mRNA-based vaccines (BNT162b2 and Spikevax) and adenoviral vector vaccines (ChAdOx1-S and Ad26.COV2.S) [7]. As a result, it's important to continuously monitor the evolution of the S-glycoprotein to identify any mutations that could promote immune evasion (Fig. **1**). When compared to the original strain, some of the so-called Variants Of Concern (VOCs), such as B.1.1.7 (alpha), B.1351 (beta), P.1 (gamma), B.1.617.2 (delta), and B1.1.529 (omicron) [8], exhibit increased transmissibility and severity [9, 10]. Consequently, this can provide some insight into the fluctuating rates of hospitalization, re-infection, and mortality that were noted throughout the several infection waves [11].

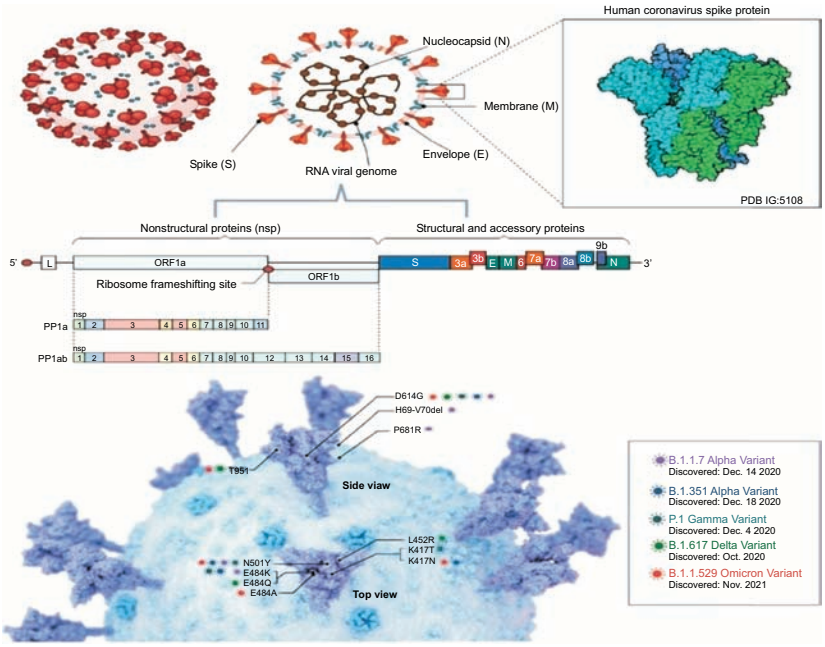

Fig. (1). The main VOC and structural characteristics of SARS-CoV-2. For every VOC, the main mutations in the S-glycoprotein are shown.

Three stages are commonly associated with the development of severe COVID-19 (Fig. **2**): (a) early infection, characterised by mild symptoms and involving the various stages of viral replication; (b) pulmonary involvement, linked to the stimulation of adaptive immunity and the predominance of respiratory symptoms; and (c) hyper inflammation, linked to immune dysregulation and often involving the Acute Respiratory Distress Syndrome (ARDS). Granted, the symptoms of SARS-CoV-2 infection vary greatly amongst individuals. Furthermore, a diurnal clinical course has been observed in COVID-19 patients, with deterioration following an initial period of recovery. This is associated with a delayed and exaggerated immune activation [12, 13]. This hyperactivation may trigger a "cytokine storm," which may be followed by lung macrophage and dendritic cell dysregulation, ultimately resulting in ARDS in these individuals [14]. Additionally, a number of inflammatory cytokines and chemokines, such as interleukin (IL)-1, IL-6, IL-7, IL-8, IL-9, and IL-10, as well as Granulocyte Colony-Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), interferon (IFN), interferon-gamma-induced protein (IP-10), Monocyte Chemoattractant Protein-1 (MCP-1), and Macrophage Inflammatory Protein-1 (MIP-1) are elevated in the blood of COVID-19 patients, especially those who require admission to an Intensive Care Unit (ICU) [15, 16]. Consequently, there are biochemical parallels between the COVID-19 hyperinflammatory response and the macrophage activation syndrome, suggesting that innate immune system targeting could be a useful strategy to lessen the severity of the condition [17].

This results in polyproteins that the viral RdRp complex's constituent parts are produced by co-translationally cleaving them with proteases that are encoded in the polyprotein. (D and E) Using the viral genome as a template, the RdRp complex produces genome-length and negativesense subgenomic RNAs. These components serve as blueprints for creating subgenomic mRNAs and complete positive-sense offspring genomes. Subgenomic mRNAs are then used to produce structural and supporting proteins. The nucleocapsid attaches to the positive-sense genomic RNA, while the structural proteins S, E, and M, derived from positive-sense subgenomic RNAs, decorate the Endoplasmic Reticulum–Golgi Intermediate Compartment (ERGIC) (H and I). Exocytosis forms a new virion and releases it from the host cell.

Widespread vaccination efforts have greatly decreased the infection's morbidity and mortality, although SARS-CoV-2 transmission continues, resulting in more hospital admissions and fatalities [18]. It follows that everyone agrees that efficient treatments will be a necessary addition to immunisation plans. Currently, only a few medications have been licensed for use against SARS-CoV-2 infection, in certain countries. These include medications to reduce

SUBJECT INDEX

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