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Drug Repurposing for Antiviral Drugs: A Review

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Review Article

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ABSTRACT

The emergence of new and pre existing viral infections has been seen all over the world in the last two centuries. At the beginning of the 21st century, humankind suffered from various viral pandemics and epidemic situations which resulted in serious public health issues that ultimately affected the world economy. Whenever there is a situation of a viral epidemic or pandemic, there is a need for rapid, safe, cost efficient, and effective drug treatment. This urgent need for an antiviral drug cannot be met by the use of the traditional drug discovery process. Also, the emergence of resistance to currently available antiviral drugs and the re emergence of new viral infections are the largest barriers to antiviral drug discovery. The medication repurposing approach is a reliable method for the discovery of rapid and cost effective drugs where new target sites and new indications for the target of approved drugs are discovered. This new perspective of antiviral medicine discovery is a promising approach to overcome the disadvantages of traditional drug discovery and process to avoid the bottleneck of antiviral drug discovery. The most encouraging outcomes of the medication repurposing strategy for treating various viral infections are discussed in this review. Repurposed drugs for various important virus families like flaviviridae, filoviridae, orthomyxoviridae, retroviruses, and corona viruses along with their pre existing use and mechanism of action are listed in this review.

INTRODUCTION

A wide variety of small microorganisms called viruses are responsible for several very Deadly Infections of Dengue Virus (DENV), Chikungunya Virus (CHIKV), West Nile Virus (WNV) Japanese Encephalitis Virus (JEV), Ebola Virus (EBOV), SARS Coronavirus (SARS-CoV), Zika Virus (ZIKV), Influenza A virus and HIV virus. Viruses are host dependent microorganism which do not encode viral replication enzyme by their own but uses the host cellular machinery for reproduction of new viral particles. In the past 30 years, many potent antiviral medications have been developed that target viral proteins or host factors [1].

Also, antiviral drugs are developed that can target six phases in the viral lifecycle; adhesion, penetration, uncoating, gene expression and replication, assembly, and replication. Although several antiviral drugs are developed but now a days there is increased demand for new antiviral agents due to

- Increased risk of chronic viral infectious diseases like Human Immunodeficiency Virus (HIV), influenza virus, and Hepatitis C Virus (HCV);
- The resurgence of many new infections like influenza viruses and coronaviruses.
- Resistance developed to the existing, narrow spectrum antiviral drugs.

The need for new antiviral medications to treat chronic infectious diseases and the emergence of new, more potent viruses serve as incentives for research into additional new targets and mechanisms for the creation of new antiviral [2].

LITERATURE REVIEW

Drug repositioning

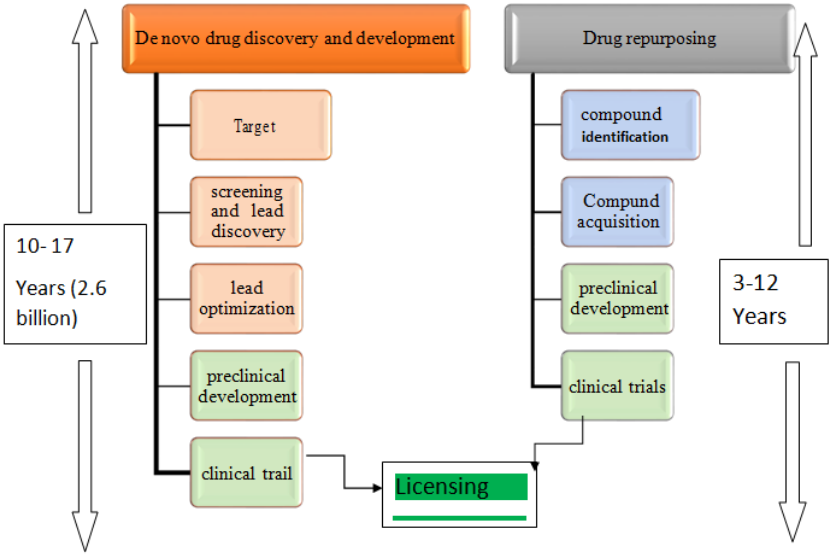
Drug repurposing, which also known as drug is repositioning, drug re tasking, drug reprofiling, drug rescuing, drug redirection, drug recycling and therapeutic switching [3]. It is a newly developed technique in which existing medications are redirected based on a viable target molecule to treat extremely rare, challenging to treat diseases and the neglected disease. In process, drug that is already on the market or in development is discovered and validated for its new therapeutic use [4]. These repurposed medications have already been tested to be safe in humans. The foundation of drug repurposing focuses on utilizing comprehensive human clinical, pharmacokinetics, and safety data as the starting point for further research in place of lengthy, dangerous, and expensive preclinical and early clinical evaluation stages. When a medicine that has already been licensed for usage is used to treat a condition that was not the drug's original target condition then it shows various advantages over the newly discovered drug by traditional method *De novo* drug discovery process Figure 1 as 1) A medicine has already undergone early stage studies and been found to be safe for use in human bodies, the likelihood of it being rejected for safety reasons is very low. 2) Because several crucial procedures, including preclinical testing, safety assessment, and, in some cases, formulation creation, have already been performed, the overall time necessary for drug development is lower. 3) Since information about the medicine is already available, any type of research into it is simpler [5].

Significance of drug repurposing

Repurposing has significant advantages over innovative medications such as a quicker start to clinical trials because the drug might already be on the market. If successful in carefully planned clinical studies, the repurposed medicine would gain the following advantages:

- Easily accessible to patients and readily available in bulk active pharmaceutical ingredient and formulation manufacturing processes.
- Less expensive than developing a new drug because the drug candidate already has safety data and only needs to prove its efficacy against the novel disease.
- Reduced time to market.
- Physicians current knowledge of the drug, its side effects, contraindications, and drug-drug interactions, which can be used to make a prescription while taking into account the patient's pre existing conditions (Figure 1).

Figure 1. *De novo* drug discovery process versus drug repurposing process.

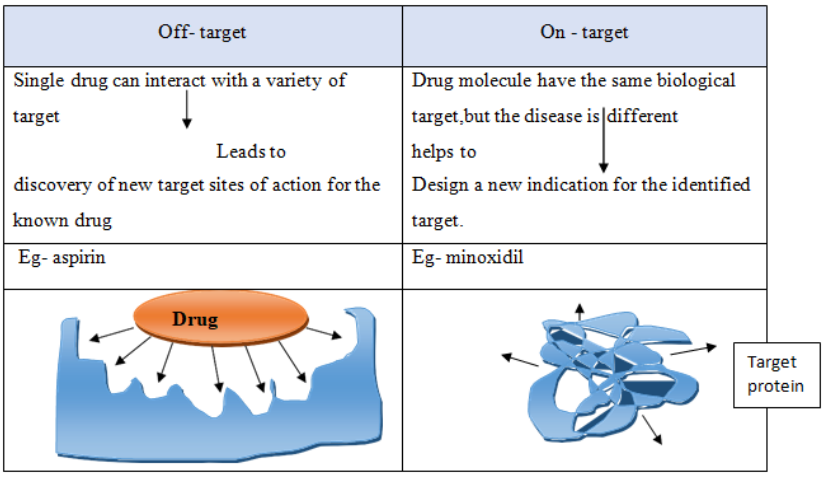


Approaches for drug repurposing

- Computational approaches: Signature matching, molecular docking, genetic association, pathway mapping, novel data sources and retrospective clinical analysis.
- Experimental approach: Phenotypic screening and binding assays to identify relevant target interaction [6].

To identify promising repurposing options for viral infectious illnesses, a therapeutic repurposing strategy combining molecular modelling techniques, such as, virtual screening, biological activity prediction and molecular dynamics simulation, has been used. Drug repurposing for antiviral drugs is possible because of following concept in Figure 2.

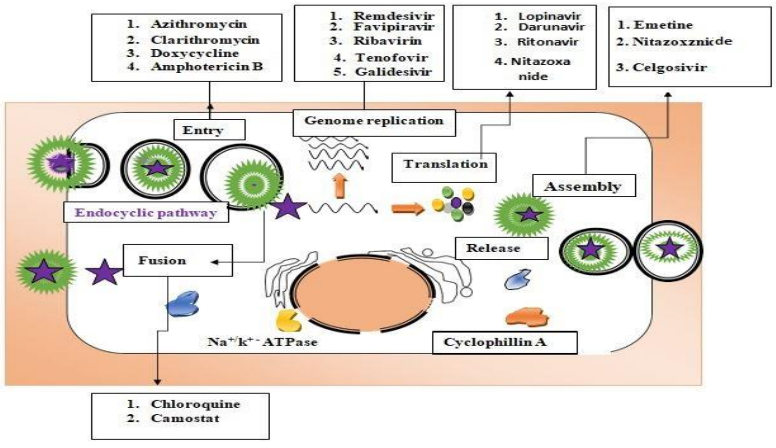
Figure 2. Strategies for drug repurposing.



Mechanism of antiviral drug repurposing

- **Direct acting antiviral:** Inhibits viral replication machinery which includes polymerase inhibitor (e.g. Remdesivir,) and viral protease inhibitor (e.g. Lopinavir/Ritonavir).
- **Host targeted antiviral:** For replication viruses use host cellular machinery so various life cycle stages of viruses within the host are considered while developing antiviral drugs. These host based antiviral drugs affect viral pathogenesis by inhibiting host cellular factors which are required for viral replication. These antiviral drugs consist of viral entry inhibitors, cellular protease inhibitors, kinase inhibitor, translation inhibitors, assembly inhibitors, release inhibitor. Repurposed antiviral drugs along with its mechanism are shown in are shown in Figure 3.

Figure 3. Stages of virus life cycle and list of repurposed drugs for specific stage.



Drug repurposing for flaviviridae

The flaviviridae are a family which consist of positive, single-stranded and enveloped RNA viruses such as zika virus, dengue virus, yellow fever, west Neil virus, and Japanese encephalitis virus. These viruses are transmitted into host *via* arthropods like mosquito or ticks. So, there is need to develop drug which can target both virus and host [7].

The zika virus, which is a flaviviruses spread by mosquitoes, was initially discovered in Uganda in 1947 in monkeys. Till a date, up to 86 countries and territories have reported evidence of zika infection led to endemic in Island of Yap, French Polynesia, Brazil.

Aedes mosquitoes, particularly aedesaegypti, are the principal vectors for the spread of the zika virus same like as in dengue, chikungunya and yellow fever infection. Zika virus infection is associated with severe inborn disabilities like neurodevelopment congenital condition and Guillain–Barre syndrome [8].

DNEV virus is 1st discovered in 1976 and its first outbreak was reported in rural areas in Central Africa amid tropical rainforests. Southeast Asia and the Americas are home to endemic DENV, which is occasionally accompanied by the emergence of new strains that have been responsible for significant epidemics since the early 2000's. Till date DNEV is endemic more than 100 countries of various continent including America, South-East Asia Africa, the Eastern Mediterranean, and the Western pacific. DENV endemic in these countries resulted into massive loss of human health. Every year, DENV infection results in 100–400 million infections, more than 500,000 hospitalizations, and 25,000 fatalities [9].

About 37 substances have been tested for their effectiveness against flaviviruses *in vivo* between 2015 and 2021; 20 of these are repurposed medications, and the majority of them exhibit broad spectrum antiviral action. Leading targets for drug development against flaviviruses are E protein, NS5 RdRp, NS2B-NS3 protease, and ER α-glycosidase. Repurposed drug for anti-DENV medication comprise chloroquine, ivermectin, lovastatin, ketotifen, faldaprevir, prochlorperazine, minocycline, metoclopramide, and N-acetylcysteine. Sofosbuvir is a very effective repurposed drug for treatment of ZIKA infection which targets the RNA dependent RNA polymerase (RdRp). Table 1 shows other repurposed drugs like emetine, niclosamide, temoporfin, novobiocin; bromocriptine also has shown desirable effects in clinical trials [10].

Table 1. Approved and investigational direct acting and host targeting antiviral with repurposed potential against Flaviviridae.

Sr. no	Drug	Category	Mechanism of action	Repurpose d for
1	Fidaxomicin	Macrolides	Inhibits RNA-dependent RNA polymerase	Zika virus
2	Neomycin	aminoglycoside antibiotic	enhance the expression of antiviral interferon-stimulated genes	Zika virus
3	Posaconazole	antifungal	targets oxysterol-binding Protein and affects intracellular cholesterol distribution and disrupt cell membrane	DENV, ZIKV
4	Chloroquine Mefloquine,	Anti-malarial drugs	Inhibits stages of replication and inhibition of RNA synthesis.	DENV, ZIKV, CHIV
5	Minocycline	tetracycline antibiotics	binds to the bacterial 30'S ribosomal subunit and interferes with protein synthesis	West Nile virus, Japanese encephalitis virus
6	Sofosbuvir	antiviral	Inhibits RNA-dependent RNA polymerase	Zika virus
7	Emetine	Antiprotozoal	Inhibits NS5 polymerase	Zika virus
8	Niclosamide	Anthelmintic	Inhibit NS2B–NS3 protease	Zika virus

9	Nitazoxanide	Antiprotozoal	Inhibits the maturation of the viral hem agglutinin and the viral transcription factor.	Zika virus
10	Novobiocin	antibiotic	Protease inhibitor	Zika virus
11	Lopinavir/Ritonavir, Nelfinavir	Antiviral drug	Protease inhibitor	DENV
12	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
13	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
14	Amphotericin-B	antifungal drugs	Inhibit the replication	JEV
15	Chlorpromazine	Antidepressant	Inhibit viral entry *via* inhibition ofclathrin-mediated endocytosis.	CHIKV, DENV, JEV, Zika
16	Imipramine	antidepressants	Entry inhibitor	CHIKV, DENV, JEV, Zika, WNV
17	Sertraline	antidepressants	Entry inhibitor	Zika virus
18	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV
19	Suramin	Antiparasitic	Entry and fusion proteins inhibition	CHIKV

Drug repurposing for filoviridae

Filoviridae family of virus includes single stranded negative sense RNA viruses. Ebola virus and Marburg virus are the important members of this family. In the Democratic Republic of the Congo, close to the river Ebola, the first case of haemorrhagic fever was reported in 1976. 2014 to 2016; West Africa saw the largest and most serious outbreak Ebola endemic. Fruit eating bats from Pteropodidae family are the critical natural hosts for EBOV virus. The virus spreads to people either directly or indirectly through intermediate zoonotic hosts, contaminated areas, infected animals, infected people's organs, or direct contact with biological fluid discharges. Acute haemorrhagic fever is the primary symptom of EBOV's deadly disease, which has a very high mortality rate (90 percent).

Another virus of Filovirus genus is Marburg Virus (MARV). As like EBOLA it is filamentous, enveloped, no segmented, negative strand RNA virus [11]. There is still no therapeutic therapy for EBOV and MARV infections that has been approved and/or is being investigated. Rehydration with electrolytes is commonly considered one of the remedies for very extremely sick individuals. Because of its high mortality rate and the lack of an efficient and FDA approved treatment, Drug repurposing strategy will produce novel, effective therapeutic approach in a smaller duration of time which will be beneficial for critical endemic condition of EBOV. Preclinical DR investigations were carried out using live viruses as well as artificial viruses, and they resulted in the discovery of a number of certified medications that could offer protection against deadly EBOV infection in experimental animals. Drugs such as teicoplanin, imipramine, chlorpromazine, chlorcyclizine, sertraline, maprotiline, and diphenylpyraline, as well as benztropine, promethazine, ketotifen, diphenhydramine, and others, may be repurposed for ebola treatment shown in Table 2.

Table 2. Approved and investigational repurposed drugs having potential against filoviridae (EBOV, Marburg).

1	Favipiravir	Influenza inhibition	Termination of RNA chain	EBOV
2	Teicoplanin	Antibiotic	Viral entry inhibitor	EBOV
3	Azithromycin	Macrolide antibiotic	Endocytosis inhibitor	EBOV
4	Brincidofovir	Human smallpox disease	-	EBOV
5	Chlorpromazine	tranquillizer	Endocytosis inhibitor	EBOV

6	Quinacrine	antimalarial	Viral entry inhibitor	EBOV

Drug repurposing for orthomyxoviridae

Influenza virus consisting influenza A (H1N1, H2N2, H5N1, H3N2, H7N9, etc.), influenza B, influenza C, influenza D belongs to Orthomyxoviridae family. These viruses are single stranded negative sense enveloped RNA viruses. Both influenza A and influenza B viruses caused severe pandemic situation in twentieth century all over world including H1N1 flu pandemic, H2N2 Asian flu epidemic, (H3N2 Hong Kong flu, H1N1 swine flu pandemic. Currently used drug which has mechanism of viral M2 ion channel inhibitor and neuraminidase inhibitors for treatment of influenza is now showing drug resistance. So repurposing is most promising technique for drug resistance influenza virus infection. Nitazoxanide, dapivirine, BAY 81-8781, clarithromycin, nalidixic acid and dorzolamide are most promising repurposed drug for influenza, whose details are given in Table 3.

Table 3. Approved and investigational repurposed drugs having potential against Orthomyxoviridae infection.

Drug repurposing for Orthomyxoviridae				
1	Clarithromycin/Naproxen	Antibacterial	Inhibition of nucleoprotein which blocks virus transcription/replication.	Influenza
2	Nitazoxanide	Antiparasitic	Maturation of hem agglutinin	Influenza
3	Dapivirine	HIV	A non-nucleoside inhibitor of HIV-1 retro transcriptase	Influenza
4	Nalidixic Acid and Dorzolamide	antibiotic	Target mutant viral neuraminidase	oseltamivir-resistant influenza

Drug repurposing for retroviruses

Reverse Transcriptase (RT), an enzyme that transforms RNA genetic material into an intermediate form of DNA, is a characteristic of retroviruses. Retroviruses have drawn a lot of attention since they are linked to serious illnesses like cancer, AIDS, and neurological conditions [12-18]. At the end of 2020, there have been an approximately 37.7 million (30.2-45.1 million) HIV positive individuals worldwide, of which over two thirds (25.4 million) reside in the WHO African Region. With 36.3 million (27.2-47.8 million) deaths caused by HIV to date, it is still a significant global public health concern [19]. Reverse transcription, integration, and maturation are three crucial stages in HIV virus life cycle that are highly consistent among members of the retroviridae family. Antiretroviral drug discovery focuses on these 3 stages of virus life cycle. Zidovudine, the first anti-HIV drug to receive FDA approval, was first created as an anti-cancer drug in the late 1960's. Zidovudine was developed as an anti-HIV formulation following a large scale library screening strategy to hasten preclinical testing. Other repurposed drugs for HIV are shown in Table 4. A significant number of host components have identified during the past two decades as possible cellular targets for anti-HIV treatments and, of special interest, for drug repurposing methods [20-29].

Table 4. Repurposed drugs for retroviruses (HIV).

1	Zidovudine	Anticancer	Reverse transcriptase inhibitor	HIV
2	Auranofin	Anti-rheumatic drug	Helps in promotion of differentiation and apoptosis of the memory $CD4^{+}$T-cell	HIV

Drug repurposing for Corona viruses

From starting of twenty first century, world is suffering from large scale epidemic and pandemics caused by highly infectious and deadly corona viruses. These Corona viruses are zoonotic viral infection which is enveloped and positive sense, single stranded RNA viruses. The crown shaped spikes on the surfaces of corona viruses give them their name. Corona viruses are divided into the alpha, beta, gamma, and delta subgroups [30-37]. In the middle of the 1960's, human coronaviruses were first discovered. The seven human infecting coronaviruses are

- 229E,

- NL63,
- OC43,
- HKU1,
- Middle East Respiratory Syndrome, or MERS.
- Severe Acute Respiratory Syndrome-1, or SARS.
- Severe Acute Respiratory Syndrome coronavirus 2 (SARS-cov-2).

Repurposed drugs for Covid 19 include polymerase inhibitors, protease inhibitors, malaria drugs, lipid lowering stains, rheumatoid arthritis drugs and some miscellaneous agents. In clinical trials, it was shown that remdesivir, a medication formerly used to treat viral illnesses like ebola and MERS-CoV, had some beneficial impacts against SARS-CoV-2. Chloroquine and hydroxychloroquine, two well-known antimalarial medications, have also been shown to be efficient against COVID-19 by reducing the viral load. List of repurposed drugs is shown in Tables 5 and 6.

Table 5. Direct acting antiviral drugs against Covid-19.

Sr.no	Drug	Mechanism of action	Original use	Repurposed for
Reverse transcription inhibitors				
1	Remdesivir	Targeting RNA-dependent RNA polymerase (Reverse transcription inhibitor)	Ebola virus infection treatment	Treatment of Covid-19
2	Favipiravir	Targeting RNA-dependent RNA polymerase	Influenza virus infection treatment	Treatment of Covid-19
3	Ribavirin	Targeting RNA-dependent RNA polymerase	Treatment of viral infections (HCV, RSV), and viral hemorrhagic fevers	Treatment of Covid-19
4	Tenofovir	Targeting RNA-dependent RNA polymerase	To treat HIV and HBV chronic infection	Treatment of Covid-19
5	Galidesivir	Targeting RNA-dependent RNA polymerase	Ebola virus disease and other viruses infections	Treatment of Covid-19
Protease inhibitors				
1	Lopinavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
2	Raltegravir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
3	Niclosamide	Protease inhibitors	To treat worm infections. Also, SARS-Corona Virus, MERS-Corona Virus, ZIKV, JEV, HCV, EBOV, HRVs, CHIKV, and EBV.	Treatment of Covid-19
4	Darunavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
5	Saquinavir	Protease inhibitors	To treat HIV infection	Treatment of Covid-19
Fusion inhibitors mimic to viral peptides and prevent the connections necessary for some enveloped viruses to fuse				
1	Camostat mesylate	Fusion inhibitor	For treatment of disseminated intravascular coagulation	Treatment of Covid-19
2	Umifenovir	Fusion inhibitor	For treatment and prophylaxis of influenza A and B infections, HCV, HBV, and ebola	Treatment of Covid-19
M2 ion channel protein blockers				
1	Amantadine	Inhibit M2 ion channel protein	Treatment of influenza infection	Treatment of Covid-19
2	Rimantadine	Inhibit M2 ion channel protein	Treatment of influenza infection	Treatment of Covid-19

Table 6. Approved and investigational host targeting antiviral with repurposed potential against Covid–19.

1	Chloroquine, HCQ	Inhibits cytokine production	Antimalarial	Treatment of Covid-19
2	Interferon β, interferon 2b	Increases immune response to viral infections by acting on target B cells through host interferon receptor and IFNAR1 signaling.		Treatment of Covid-19
3	Tocilizumab	Reduce cytokine response of host by binding and inhibiting IL-6 receptor	Rheumatoid arthritis	Treatment of Covid-19
4	Dexamethasone	Glucocorticosteroid with anti-inflammatory and immunosuppressant effect		Treatment of Covid-19
5	Statins	Lipid lowering drugs with anti-inflammatory and Immunomodulatory properties.		Treatment of Covid-19
6	Losartan and its derivatives/ARBS	Angiotensin receptor blockers	Antihypertensive	Treatment of Covid-19
7	Ruxolitinib, Baricitinib	JAK inhibitor	Inflammatory and autoimmune diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease	Treatment of Covid-19

DISCUSSION

Challenges for antiviral drug discovery

- One drawback is that the antiviral effect seen *in vitro* is frequently not reproducible *in vivo*.eg- Lopinavir/Ritonavir, which suppressed Covid-19 in cultured cells but could not provide an advantage above standard therapy in patients when administered alone.
- Even though the efficient and promising outcomes in animal models cannot ensure efficacy in humans. Eg: The use of remdesivir to treat EBOV disease and Chloroquine to treat dengue fever.
- Broad spectrum antiviral is needed for drug repurposing as narrow spectrum antiviral drugs are not suitable.
- Drug safety in one disease condition may or may not guarantee the same safety in other disease conditions.
- Drug resistant for both direct acting and host targeting antiviral is the bottleneck for antiviral drug repurposing.

CONCLUSION

Although viral infections are acknowledged as a worldwide public health concern, most of them still lack effective vaccinations and effective antiviral medicines also the discovery of new specific antiviral needs a high cost and more time. Since now a day's strategy of discovering repurposed medications are an efficient way in case of discovering an urgent and cost-effective treatment for newly emerging viral infections as repurposed drugs have already undergone extensive testing (for toxicity, pharmacokinetics, pharmacodynamics, dosage, etc.) for their original indication. Repurposing them also reduces the clinical risks and requires comparatively less money and time. Drug repurposing has already shown very beneficial results with the pharmaceuticals that have been effectively repurposed, and this strategy can increase the opportunity to address the difficulties with resistance to antiviral and new viral threats. This article provides a summary of the effectiveness of numerous medications, categorized according to their mechanisms of action, against a variety of severe viral illnesses. Repurposed medications for a number of significant virus families, including the flaviviridae, filoviridae, orthomyxoviridae, retroviruses, and Corona viruses, are included in this review along with their prior usage and mechanisms of action. The medication repurposing strategy has produced candidates that show efficient effects in treating a variety of viral infections and can also be further investigated to get around the drug discovery barrier for newly emerging and re emerging viral contagious diseases.

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REFERENCES

1. Mani D, et al. Drug Repurposing in Antiviral Research: A Current Scenario. J Young Pharm. 2019;11:117.
2. Lou Z, et al. Current progress in antiviral strategies. Trends Pharmacol Sci. 2014;35:86-102.
3. Gelosa P, et al. Drug repurposing in cardiovascular diseases: Opportunity or hopeless dream? Biochem Pharmacol. 2020;177:113894.
4. Pareek S, et al. Chapter 6 the success story of drug repurposing in breast cancer. In book: Drug repurposing in Cancer therapy. 173-190.
5. Sudhir A, et al. *In Silico* Approaches for Drug Repurposing for SARSCoV-2 Infection. R Soc Chem. 2022.
6. Sarwar SB, et al. Assessing drug repurposing option for emerging viral Diseases: Concerns, solutions, and challenges for forthcoming viral battles. J Adv Biotechnol Exp Ther. 2021;4:74-94.
7. Guha M, et al. Repositioning existing drugs for cancer treatment. Pharm J. 2015;294:7867.
8. Li X, et al. Strategy, Progress, and Challenges of Drug Repurposing for Efficient Antiviral Discovery. Front Pharmacol. 2021;12:660710.
9. Ji X, et al. Medicinal chemistry strategies toward host targeting antiviral agents. Med Res Rev. 2020;40:1519-1557.
10. Chan S, et al. Current and Future Direct Acting Antivirals against COVID-19. Front Microbiol. 2020;11.
11. Rita M, et al. Baric, Developing therapeutic approaches for twenty first century emerging infectious viral diseases. Nature Med. 2021;27:401–410.
12. Song B, et al. Zika virus: History, epidemiology, transmission, and clinical presentation. J Neuroimmunol. 2017;308:50-64.
13. Messina J, et al. Global spread of dengue virus types: Mapping the 70-year history. Trends Microbiol. 2014;22: 138-146.
14. Ferreira AC, et al. Sofosbuvir protects Zika virus infected mice from mortality, preventing short and long term sequelae. Sci Rep. 2017;7:9409.
15. Kimura H, et al. Ebola virus disease: A literature review. J Coast Life Med. 2015;3:85-90.
16. Nascimento IJ, et al. Drug Repurposing: A Strategy for Discovering Inhibitors against Emerging Viral Infections. Curr Med Chem. 2021;28:2887-2942.
17. Bai JP, et al. Drug repurposing for Ebola virus disease: Principles of consideration and the Animal Rule. J Pharm Sci. 2019;108:798-806.
18. Mercorelli B, et al. Drug Repurposing for Viral Infectious Diseases: How Far Are We?. Trends Microbiol. 2018;26:865-876.
19. Pizarro A, et al. Drug Repurposing Approaches for the Treatment of Influenza Viral Infection: Reviving Old Drugs to Fight against a Long-Lived Enemy. Front Immunol. 2019;10.
20. Simon V, et al. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. The Lancet. 2006;368:489-504.
21. Margaret A, et al. The efficacy of Azidothymidine in treatment of patients with AIDS and AIDS Related complex. N Eng J Med. 1987;317:185-191.
22. Bedair A, et al. Insights into the FDA 2018 new drug approvals. Curr Drug Discov Technol. 2019;16:1.
23. Yamashita M, et al. Capsid Dependent Host Factors in HIV-1 Infection. Trends Microbiol. 2017;25:741–755.
24. Abdulaziz L, et al. Bashir A Yousef, Antiviral Activity of Approved Antibacterial, Antifungal, Antiprotozoal and Anthelmintic Drugs: Chances for Drug Repurposing for Antiviral Drug Discovery. J Exp Pharmacol. 2022:14 97–115.
25. Yuan J, et al. Antibiotic Fidaxomicin is an RdRp inhibitor as a potential new therapeutic agent against Zika virus. BMC Med. 2020;204.
26. Namasivayam V, et al. Repurposing drugs targeting epidemic viruses. Drug discovery. 2022;27:1874-1894.
27. Trivedi J, et al. Drug Repurposing Approaches to Combating Viral Infections. J Clin Med. 2020;9:3777.
28. Ganesan S, et al. Quercetin inhibits rhinovirus replication *in vitro* and *in vivo*. Antiviral Res. 2012;94:258–271.
29. Burt FJ, et al. Chikungunya virus: An update on the biology and pathogenesis of this emerging pathogen. Lancet Infect Dis. 2017;17:107–117.

30. Shim A, et al. Therapeutic and prophylactic activity of itraconazole against human rhinovirus infection in a murine model, Sci Rep. 2016;6:23110.
31. Nandan Kumar, et al. Repurposing of approved drug molecules for viral infectious diseases: A molecular modelling approach. J Biomol Struct Dyn. 2021.
32. Vaishnavi R, et al. Drug Repurposing in Antiviral Research: A Review. Int J Innov Res Technol. 2021;8:387-392.
33. Ashour NA, et al. A Systematic Review of the Global Intervention for SARS-CoV-2 Combating: From Drugs Repurposing to Molnupiravir Approval. Drug Des Devel Ther. 2022;16:685–715.
34. Shea R, et al. Repurposing Psychotropic Agents for Viral Disorders: Beyond Covid. Assay Drug Dev Technol. 2021.
35. Singh TU, et al. Drug repurposing approach to fight COVID-19. Pharmacol Reports. 2020;72:1479–1508.
36. Farias KJS, et al. Antiviral Activity of Chloroquine against Dengue Virus Type 2 Replication in Aotus Monkeys. Viral Immunol. 2015;28:161–169.
37. Saul S, et al. Old Drugs for a New Virus: Repurposed Approaches for Combating COVID-19. ACS Infect Dis. 2020.