DRUG REPURPOSING: AN EMERGING APPROACH TO DRUG DISCOVERY

By

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ABSTRACT

Drug repurposing is a powerful tool for future medicine, through the process of discovering new uses for existing drugs. Drug repurposing drastically cuts the time and expense involved in developing new medications by utilizing safety profiles and efficacy data that are currently available. In a diverse population of humans, people have unique sets of inherited or non-inherited genetic abnormalities that result in certain individuals responding less or not to all general treatments or drugs. Medicines that have been approved may not be suitable for a person because of the deficiency of a specific target. This situation leads to the requirement of personalized medicines. Reduced lack of efficacy drug repurposing approach has a significant role, which results in best medicine accompanied by low toxicity and high efficacy. This is achieved together with the advancement of next-generation sequencing technologies and personalized genomic studies can be conducted with an affirmative approach. Prospects include advancements in artificial intelligence, big data analytics and other technologies, focusing on rare diseases, combining repurposed drugs with other medications or novel drugs, and in the development of personalized medicines. Drug repurposing is exciting and fast-developing and possesses the potential to completely change the pharmaceutical industry's approach to the development of medications.

Keywords: Drug Repurposing, Drug Discovery, Medications, Genomic Studies, Artificial Intelligence, Big Data Analytics, Personalized Medicines.

INTRODUCTION

Drug repurposing, also known as drug repositioning or drug reprofiling, is an unconventional drug discovery approach to discovering new therapeutic uses for the existing drugs that are already approved or may be in various stages of development. With the aid of this approach, time and resources can be reduced compared to developing entirely new drugs. The reports state that about 30–40% of new drugs approved by the US Food and Drug Administration (FDA) between 2007 and 2009 are considered repurposed drugs. A study found that 35% of transformative drugs approved by the FDA between 1984 and 2009 possess both innovative and groundbreaking effects on patient care (Graul et al., 2010).

From concept to market, the total cost of producing a new drug is to be $1.8 to $2.6 billion. Additionally, the entire process will take 10–17 years also. Approval of drugs through the repurposing is expected to take 3–12 years and cost $40–80 million, which is comparatively lesser than the traditional method of drug development (Xue et

al., 2018). Studies state that about 30% of repurposing techniques are successful and result in a product approved for marketing, compared to 10% for drugs developed through the traditional route. However, others conclude contradictorily that repurposed drugs don't succeed more often than new agents. According to the recent evaluations, pharmaceutical industries have notably placed the market for repurposed drugs at $24.4 billion in 2015 with an elevated growth up to $31.3 billion in 2020 (Rudrapal et al., 2020).

Repurposing strategy received renewed attention during the COVID-19 pandemic after the FDA granted Emergency Use Authorization (EUA) for several repurposed drugs to treat COVID-19. Within six months of the start of the pandemic, the FDA granted EUA for remdesivir to treat COVID-19, sold under the name Veklury, which is a broad-spectrum antiviral drug intended for the treatment of RNA-based viruses, and evaluated for use against the Ebola virus, but Remdesivir had not received FDA approval for an indication prior to its authorization as a COVID-19 treatment (Eastman et al., 2020). Figure 1 shows drug repurposing.

1. Literature Review

Krishnamurthy et al. (2022) systematically reviewed the root causes, barriers, and facilitators of drug repurposing. The study identified that promising drugs are often abandoned due to insufficient efficacy, strategic business decisions, safety issues, and regulatory challenges. Rudrapal et al. (2020) explored the concept of drug repurposing, which involves identifying new therapeutic uses for existing drugs. This strategy is highlighted as a cost-effective, time-saving, and lower-risk alternative to traditional drug discovery methods.

Rao et al. (2022) explored the concept of drug repurposing as an efficient alternative to traditional drug discovery. The study highlighted the economic and risk-reducing benefits of repurposing existing drugs, which have already been approved for safe use in humans.

Kulkarni et al. (2023) explored the concept of drug repurposing, which involves using existing drugs for new therapeutic purposes. This approach gained significant attention during the COVID-19 pandemic due to its potential to expedite the drug discovery process and address urgent healthcare needs.

Bhagat and Butle (2021) discussed the potential of drug repurposing as a cost-effective and time-efficient strategy in drug development. The authors highlight the challenges of traditional drug development, such as high costs and low success rates, and propose drug repurposing as a solution to these issues.

Bellera et al. (2021) explored the growing interest in drug repurposing, highlighting its potential to shorten drug development timelines and reduce costs. The study discussed the advantages of repurposed drugs, such as their established safety profiles, and the challenges, including intellectual property issues and data accessibility.

Sun et al. (2022) provided a comprehensive bibliometric analysis of drug repurposing publications from 2010 to 2020. Utilizing data from the Science Citation Index Expanded (SCI-E) and Social Sciences Citation Index (SSCI) databases, the study highlights the historical development, major contributors, and research trends in drug repurposing.

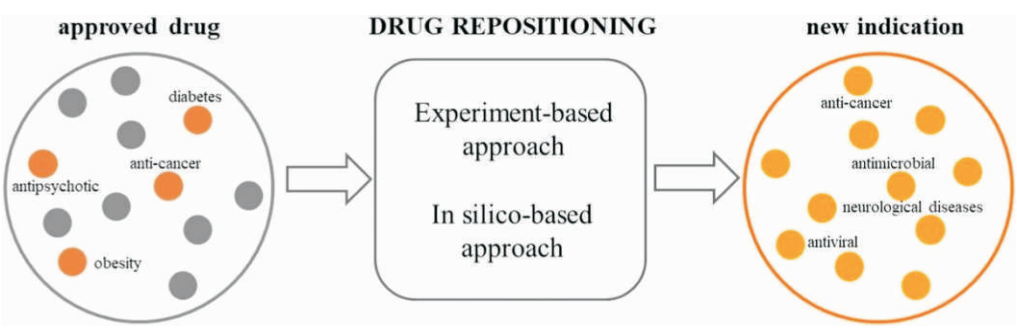


Figure 1. Drug Repurposing

2. Traditional Drug Discovery versus Drug Repurposing

2.1 Traditional Drug Discovery

- *Preclinical Research and Discovery (Average Duration: 6.5 Years):* This stage includes a typical 30-day safety evaluation, examining the drug to confirm safety through animal testing.
- *Phase 1 Clinical Research (Average Duration: 1.5 Years):* This first phase of human trials primarily focuses on the drug's safety, and its pharmacokinetic and pharmacodynamic properties.
- *Phase 2 Clinical Research (Average Duration: 2 Years):* These studies are relatively small-scale and involve patients with the target disease or condition.
- *Phase 3 Clinical Research (Average Duration: 3.5 Years):* This phase is conducted if the drug proves safe during the second phase.
- *Phase 4 Clinical Research (Average Duration: 1.5 Years):* The FDA has already approved the drug. This phase is commonly referred to as post-marketing surveillance (Hughes et al., 2011).

2.2 Drug Repurposing

- *Identification of Compounds (1.2 Years):* Selecting a potential medication for a specific therapeutic target within the human body.
- *Purchasing a Compound (0–2 Years):* Acquiring licenses for the novel therapeutic candidate.
- *Development (1–5 Years):* This process begins with preclinical research and continues through Phase 1 or Phase 2 drug trials.
- *The FDA's Post-Purchase Safety Study:* After a product is made available for widespread use, the FDA continues to monitor the safety of all medications and devices (Kulkarni et al., 2023).

3. Approaches of Drug Repurposing

3.1 Drug-Based Approach

This method is preferred when extensive data regarding the particular drug is available. It may be either target-oriented or off-target-oriented (Rao et al., 2022). In on-target drug repurposing, the known target is associated with a disease different from the drug's original indication (e.g., sildenafil, originally used for the treatment of angina, was repurposed for erectile dysfunction). Off-target drug repurposing is based on drug promiscuity, or more aptly, polypharmacology, where the drug acts on multiple targets, allowing secondary targets to be used as new indications (e.g., cimetidine, a peptic ulcer drug, repurposed for lung cancer).

3.2 Disease-Based Approach

In a disease-based approach, repurposing efforts begin with the symptoms, pathophysiology, and mechanism of a particular disease. This method is preferred when a specific disease is under focus or if the data regarding the drug is inadequate.

3.3 Target-Based Approach

A target-based approach implies a new indication without a treatment, with an established drug known as the target; the old and new indications typically differ quite significantly. This includes the investigation of the specific molecular targets that are implicated in the pathology of a disease and using the existing drug proven to modulate those targets (Parisi et al., 2020).

4. Drug Repurposing in Various Diseases

4.1 Drugs Repurposed For Cancer

The second-greatest cause of death globally and a significant public health issue is cancer. Cancer is the leading cause of morbidity and mortality. Those 60 years of age and younger accounted for about 57% of newly diagnosed cases and 47% of cancer-related fatalities. There will be a 60% rise in cancer burden (Nolen et al., 2017). In the context of cancer therapy, this method makes use of the medications established safety profiles, which have already undergone extensive research for other issues. For instance, drugs may have anticancer properties due to their effects on cell signaling, apoptosis, or angiogenesis.

4.1.1 NSAIDs Repurposed For Cancer Therapy

One of the best examples of drugs repurposed for cancer are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Tumor-promoting inflammation is one of the characteristics of cancer that reveals a connection between the inflammation process and tumor

progressions and development. NSAIDs include ibuprofen, aspirin, mefenamic acid, celecoxib, and diclofenac. These drugs show the anti-inflammatory effect by their ability to block the cyclooxygenase (COX) or prostaglandin endoperoxide H synthase (PGHS) (Wong, 2019). Figure 2 shows the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

4.1.2 Antidiabetics Repurposed For Cancer Therapy

Antidiabetic agents, including sulfonyl ureas, biguanides, and thiazolidine diones, show beneficial repurposing activity for the treatment of cancer. Antidiabetic agents are used for cancer treatment because of the metabolic links between the two diseases that include hyperglycemia, hyperinsulinemia, inflammation, obesity, and oxidative stress (Olatunde et al., 2021).

The use of the metformin drug shows that it inhibits complex I mitochondrial respiratory tract chain. The consequence is the activation of a cellular regulator of energy homeostasis, i.e., AMP-activated protein kinase (AMPK), which is a tumor suppressor.

Thiazolidinediones include rosiglitazone and pioglitazone, and they possess anti-tumor activities by binding and activating the peroxisome proliferator-activated receptor (PPAR) and inhibiting the differentiation and apoptosis of normal and tumor cells.

Sulfonyl Ureas (SU) includes gliclazide and glyburide, and it exerts antiproliferative effects by inhibiting cell growth, influencing tumor cell metabolism, and induced ROS production, leading to cancer cell death. Preclinical studies suggest that SU has potential benefits in treatments of breast, pancreatic, and colorectal cancer. Figure 3 shows the antidiabetic agents.

4.1.3 Antihyperlipidaemic Drugs Repurposed For Cancer Therapy

Worldwide, Prostate Cancer (PC) is the second most frequent cancer among men and the fifth leading cause of death. Moreover, standard treatments for PC pose several issues, including side effects and mechanisms of

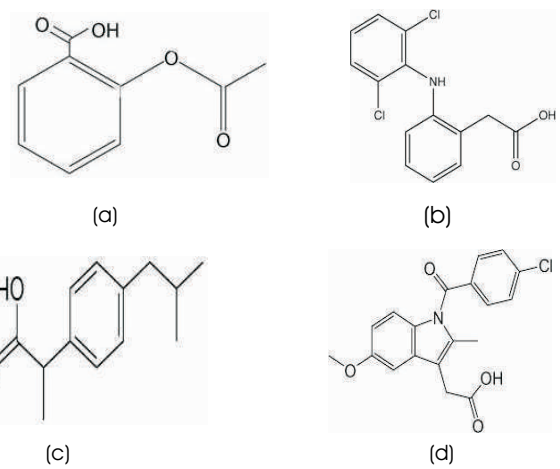


Figure 2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (a) Aspirin, (b) Diclofenac, (c) Ibuprofen, (d) Indomethacin

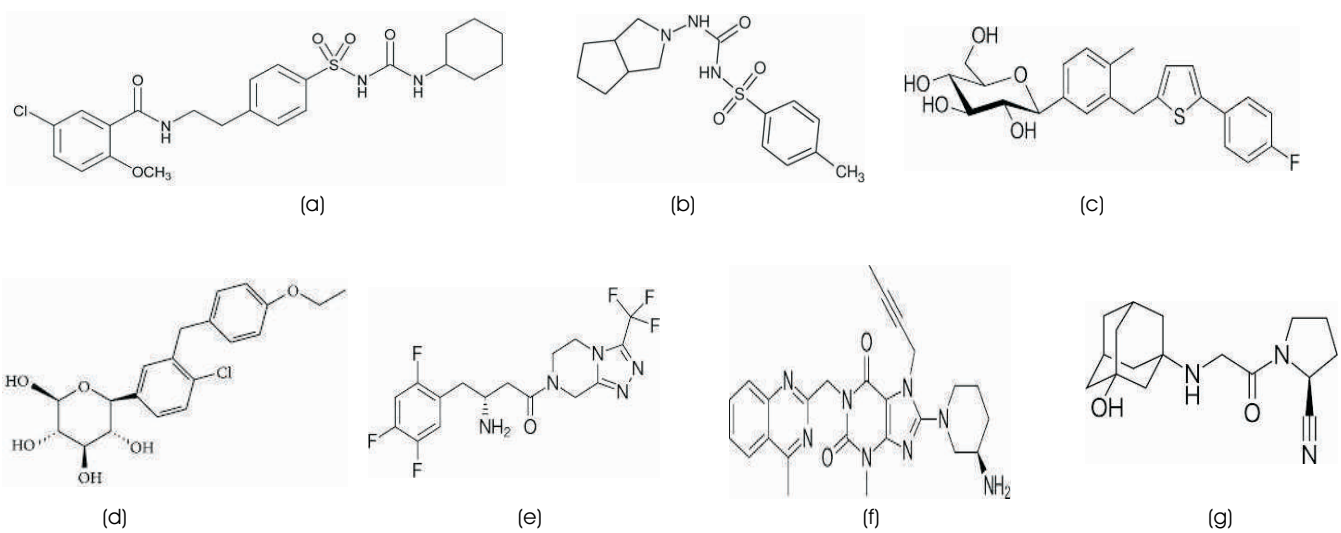


Figure 3. Antidiabetic Agents (a) Gliburide, (b) Gliclazide, (c) Dapaglifozin, (d) Canaglifozin, (e)Sitagliptin, (f) Linagliptin, (g) Vildagliptin

resistance. The severity of PC depends on the level of circulating androgenic hormones, mainly testosterone, which is a cholestrol derivative. Patients associated with PC have a high cholesterol level because PC cells depend more on endogenous production of cholesterol than dietary cholesterol, so men with a high cholesterol level are more susceptible to PC. So, statins are antidyslipidemic drugs that inhibit 3-hydroxymethyl butyryl coenzyme A (HMGCoA) reductase and block mevalonate (cholestrol precursor) production. Statins reduce serum cholesterol, and in vitro and in vivo studies indicate that they reduce the progression of prostate cancer and decrease tumor volume and serum levels of Prostate-Specific Antigen (PSA). Statins repurposed for PC are Atorvastatin, Simvastatin, Fluvastatin, Mevastatin, Lovastatin, and Rosuvastatin, which are administered as monotherapy or combination (Hamilton et al., 2008). Figure 4 shows the antihyperlipidaemic drugs.

4.2 Drugs Repurposed in Parkinson's Diseases

Neurological diseases pose a burden on worldwide health. These are devastating diseases that primarily affect the brain, spinal cord, cranial nerves, and peripheral nerves. The estimates show that neurological diseases are included in the Global Burden of Disease (GBD) study. Parkinson's disease (PD) affects the quality of life and is a high economic burden for health systems. PD

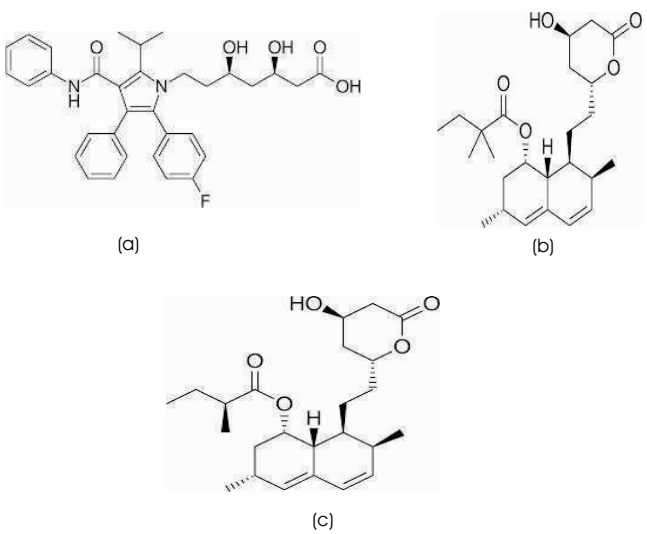


Figure 4. Antihyperlipidaemic Drugs (a) Atorvastatin, (b) Simvastatin, (c) Lovastatin

is characterized by the progressive degeneration of dopaminergic neurons of the substantia nigra and pars compacta (SNpc) or the presence of Lewy bodies (Meade et al., 2019). Through drug repurposing techniques, this study offers safe and effective treatments for PD.

4.2.1 Anti Diabetic Agents Repurposed for Parkinson's Disease

Exenatide belongs to a group of glucagon-like peptide I receptor agonists of anti-diabetic agents. In studies, exenatide shows support for dopamine cell function, thereby reducing inflammation, improving neuron energy function, and switching on neuron survival signals. Metformin can rapidly penetrate the BBB and provide neuroprotective action against stroke, cognitive impairment, reducing alpha synuclein phosphorylation and aggregation, and influencing cellular processes associated with age-related conditions, including inflammation and autophagy; all of these are responsible for the pathogenesis of PD (Li et al., 2022).

4.2.2 Antiepileptic Drugs Repurposed For PD

Zonisamide shows better efficacy in various neurological and psychiatric diseases such as migraine, neuropathic pain, essential tremor, and Parkinson's disease. Block sodium and T-type calcium channels, inhibition of carbonic anhydrase, inhibition of glutamate release, and modulation of the GABA A receptor. Levetriacetam has a promising potential for the treatment of PD. Mainly, it eases the levodopa-induced dyskinesias without worsening PD motor function.

4.2.3 Tetracyclines Repurposed For PD

Tetracyclines are said to be neuroprotective. Doxycycline is a tetracyclic antibiotic that shows neuroprotective effects. Initially proposed as having anti-inflammatory properties similar to those of minocycline. Doxycycline exerts neuroprotective action by inhibiting amyloid aggregation and fibril formation of amyloid beta (Ab), prion protein (PrP), β microglobulin, and alpha-synuclein. Figure 5 shows the drugs repurposed in Parkinson's diseases.

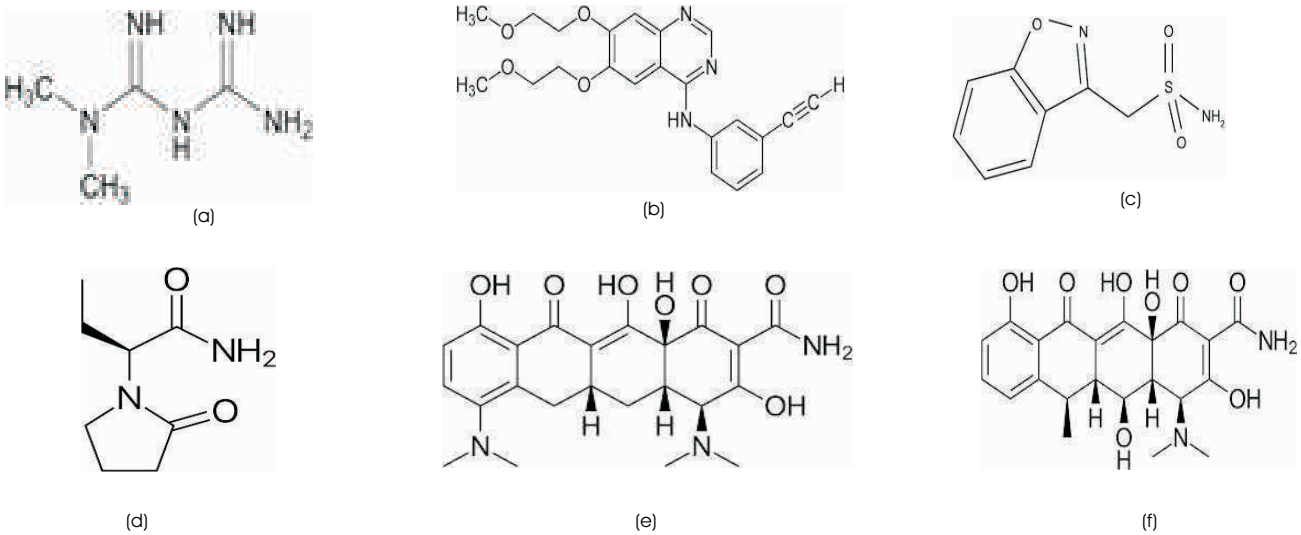


Figure 5. Drugs Repurposed in Parkinson's Diseases (a) Exenatide, (b) Metformin, (c) Zonisamide (d) Levetriacetam, (e) Minocycline, (f) Doxycycline

4.3 Drugs Repurposed For COVID 19

The 21st-century human population is enduring a widespread pandemic of highly pathogenic coronaviruses, which caused severe acute respiratory syndrome coronavirus (SARS-CoV2) in 2019–2020, middle east respiratory syndrome coronavirus (MERS-CoV) in 2012, and acute respiratory syndrome coronavirus (SARS-CoV) in 2002–2003 (Sharma et al., 2020). The pandemic situation of COVID-19 needs an urgent development of potential strategies for the development in order to protect the people who are suffering the COVID-19 pandemic. But the development and discovery of drugs is such a lengthy and tedious process. So in order to avail the novel drugs for COVID-19, clinical trials are done on various drugs. WHO identified that some therapies and researchers believed that these are most promising for the treatment of COVID-19.

Chloroquine and hydroxychloroquine are drugs coming under the category of anti-parasite drugs that were repurposed for the treatment of COVID-19. USFDA gave emergency approval for these drugs in March 2020 (Lei et al., 2020). Clinical trials suggest that hydroxychloroquine can be used for treatment of COVID-19 or in combination with the macrolide antibiotic azithromycin. New York State did a study and found out that there is no benefit seen with hydroxychloroquine or with azithromycin. Hydroxychloroquine poses cardiac toxicity, and on looking on to these adverse effects, in June 2020, these drugs were withdrawn.

Antiviral drugs such as favipiravir, remdesivir, and lopinavir were previously clinically for the treatment of SARS, MERS, and AIDS. A fore mentioned drug was not approved by the FDA. But in 2020 it is used as emergency use authorization (EUA) for the treatment of COVID-19 (Eastman et al., 2020). Recently reported that there was clinical improvement in 68% of patients after the administration of remdesivir.

Ribavirin is a broad-spectrum antiviral drug, and a combination of ribavirin with ritonavir or lopinavir reduces the risk of ARDS and death in SARS patients. Further clinical trials on favipiravir state that it is more therapeutically active than lopinavir and ritonavir.

Human monoclonal antibody-based drug Sarilumab inhibits the interleukin-6 (IL-6) receptor, and it is used for the management of COVID-19. Tocilizumab is also a recombinant human monoclonal antibody that inhibits the IL-6 receptor. It is used in COVID-19 patients suffering with elevated levels of IL-6 and cytokine storms. Figure 6 shows the drugs repurposed for COVID 19.

4.4 Drugs Repurposed For Zika Infection

Zika virus is a mosquito-borne illness caused by Zika virus. It is primarily transmitted through the bites of infected Aedes

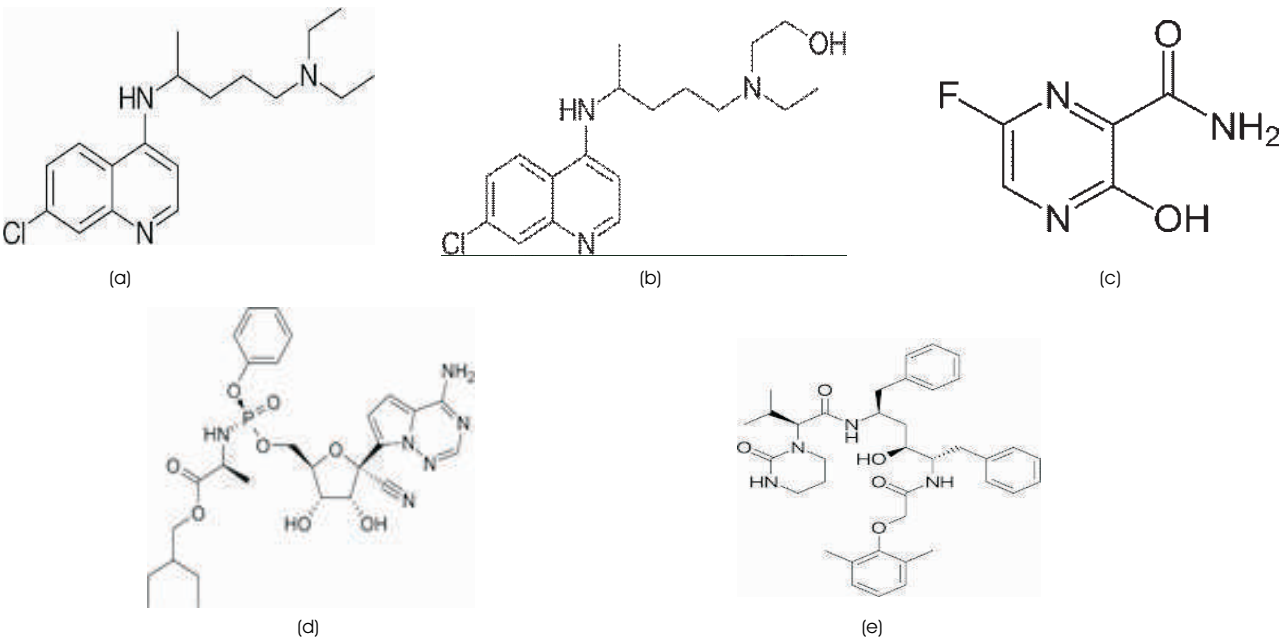


Figure 6. Drugs Repurposed For COVID-19 (a) Chloroquine, (b) Hydroxychloroquine, (c) Favipiravir, (d) Remedisvir, (e) Lopinavir

mosquitoes, particularly Aedes aegypti and Aedes albopictus. Zika virus disease is associated with severe birth defects and Gullain-Barre syndrome. This viral disease lacks an effective antiviral agent and vaccines for the treatment. ZIKV was first isolated in April 1947 from the serum of a pyrexial rhesus monkey in Uganda. Second isolation occurs in January 1948, as the serological studies indicate that there is possible transmission to humans, and this was confirmed rapidly (Talero-Gutiérrez et al., 2018). The main symptoms associated with ZIKV are rashes, fever, conjunctivitis, and athralgia. WHO declared ZIKV a public health emergency in early 2016.

Researchers identified FDA-approved drugs and bioactive molecules that inhibit Zika virus (ZIKV) replication. Daptomycin and mycophenolic acid are promising candidates for treating ZIKV during pregnancy due to their ability to cross the placenta and safety profile.

Niclosamide and azithromycin showed potent inhibition of ZIKV in neural cell lines. Further studies revealed novobiocin, niclosamide, and temoporfin as novel inhibitors targeting the NS3/NS2B protease.

Nanchangmycin, a bacterial polyether, demonstrated antiviral activity against ZIKV in various cell lines and midbrain neuron-glia cultures. Hippeastrine hydrobromide, a natural alkaloid, inhibited ZIKV replication and microcephaly-associated effects with lower toxicity compared to other antiviral drugs.

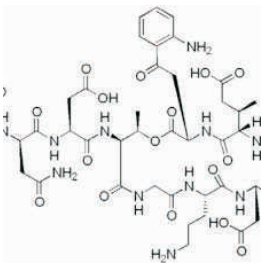
Ivermectin, an anti-parasitic drug, inhibits ZIKV replication, reduces viral load, and prevents neuronal damage in mice, but was found ineffective against the Senegal strain of ZIKV.

Doxycycline, a tetracycline antibiotic, shows promise against ZIKV by reducing viral load and replication and potentially preventing brain damage like microcephaly.

Sertraline, an antidepressant, has been found to interfere with ZIKV replication by targeting viral proteins involved in replication.

Chloroquine inhibits ZIKV infection in vitro and in animal models by preventing viral entry and replication. Hydroxychloroquine exerts similar activity against ZIKV, while amodiaquine targets viral proteins, offering potential for overcoming chloroquine resistance. Other antimalarial drugs like mefloquine, primaquine, and lumefantrine are being explored for potential effectiveness against ZIKA. Figure 7 shows the drugs repurposed for Zika infection.

4.5 Drugs Repurposed For Ebola Infections



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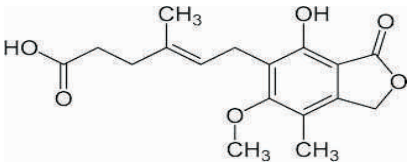

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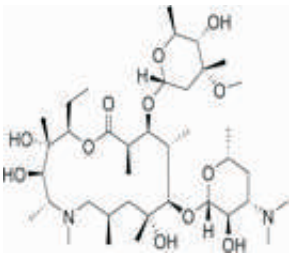

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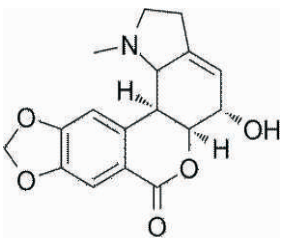

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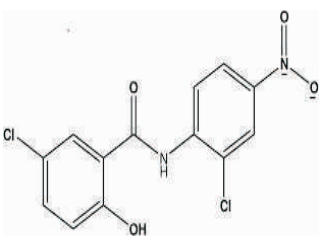

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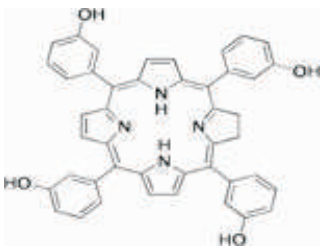

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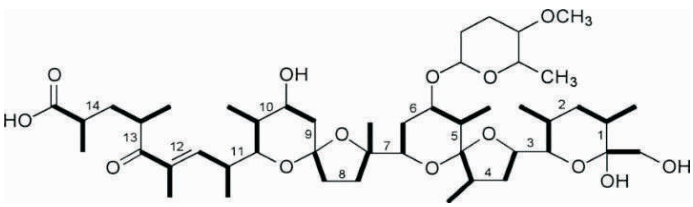

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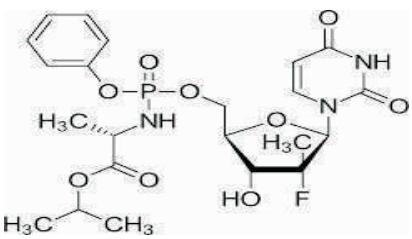

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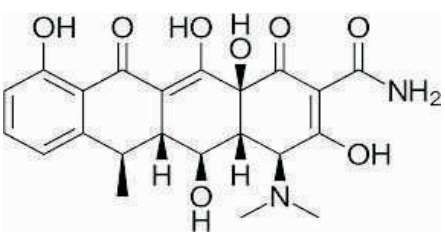

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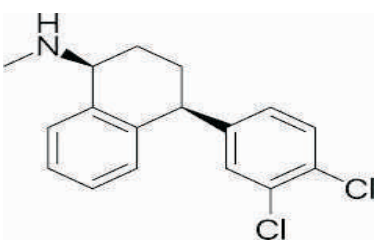

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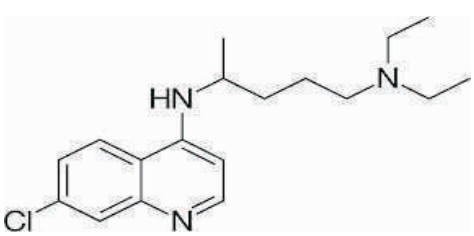

(i)

(m)

Figure 7. Drugs Repurposed for Zika Infection (a) Daptomycin, (b) Mycophenolic Acid, (c) Azithromycin, (d) Hippeastrine, (e) Niclosamide, (f) Temoporfin, (g) Nanchangmycin, (h) Sofosbuvir, (i) Ribavirin, (j) Ivermectin, (k) Sertraline, (l) Chloroquine, (m) Hydroxychloroquine

Ebola Virus Disease (EVD), previously known as Ebola hemorrhagic fever, is a severe and fatal illness affecting humans and nonhuman primates. Infection is caused by one of the five identified ebola virus species, of which the Zaire ebola virus is mainly responsible for the majority of the outbreaks and fatalities. Ebolavirus is a member of the Filoviridae family. The Ebola virus spreads through direct contact with blood, secretions, or the body fluids of infected animals or people. The primary hosts of the ebola virus are wild animals such as bats and monkeys, and humans get infected by handling infected animals or consuming their meat, and secondly, the virus can spread from person through direct contact with body fluids such as blood, vomit, saliva, diarrhea, and semen. EBOV is responsible for several outbreaks in the late 1970s, but the last one is in 2014-2016, which is the most alarming due to its size and spread of infection.

There are no licensed drugs or broadly active vaccines available for the treatment of EBOV. Treatment of EBOV-infected patients with some drugs is associated with a decreased fatality rate compared to other patients; however, clinical studies should be conducted to assess the efficacy (Namasivayam et al., 2022).

The most promising anti-EBOV activity is found on Selective Estrogen Receptor Modulators (SERM), i.e., toremifene and clomiphene, which have shown promising potential in the treatment of ebola viral disease. Research indicates that they disrupt the virus's ability to enter and infect the cells.

Potential activity of chloroquine in EBOV is achieved by inhibiting the entry of virus to host cells. This is achieved by inhibition of vesicle sorting and endosome membrane fusion and by increasing endosomal pH. Chloroquine inhibits EBOV in various cell lines.

Amodiaquine is another anti-malaria drug that is structurally related to chloroquine, which is widely used in Africa (Johansen et al., 2013). Amiodarone, an anti-arrhythmic drug, shows antiviral activity against the Ebola virus by inhibiting viral entry and replication but requires larger trials for safety and efficacy.

Sertraline, an antidepressant, has preclinical evidence of effectiveness against the Ebola virus, potentially inhibiting viral replication and spread.

Bepridil, a calcium channel blocker, and sertraline both effectively inhibit Ebola virus in vitro by over 90%.

Favipiravir, a viral RNA polymerase inhibitor, has broad-spectrum antiviral activity against RNA viruses, including Ebola, by causing lethal mutagenesis.

Azithromycin, a macrolide antibiotic, shows promise against Ebola virus but lacks direct antiviral inhibitory effect and requires further research.

BCX-4430 (Galidesivir), a novel antiviral drug, specifically inhibits RNA-dependent RNA polymerase, an enzyme necessary for RNA virus replication, showing promise against Ebola virus disease. Figure 8 shows the drugs repurposed for Ebola infections.

5. Prospectives of Drug Repurposing

Drug repurposing consists of finding new therapeutic uses of old drugs from original medical indications. The de nova drug discovery process requires an average of about 17 years and $ 2.5 billion to approve a drug. Drug repurposing gained attractive attention to speed up the drug discovery process. However, technological advances have enabled more systemic approaches to drug repurposing.

The example is COVID-19, which arose in 2019 and affected worldwide 1,77,00000 individuals. To improve the health conditions of hospitalized patients and minimize the outbreak severity, no possible drugs are there. Repurposing strategy received renewed attention during the COVID-19 pandemic after the FDA granted Emergency Use Authorization (EUA) for several repurposed drugs to treat COVID- 19.Within six months of the start of the pandemic, the FDA granted EUA for remdesivir to treat COVID-19, sold under the name Veklury, which is a broad-spectrum antiviral drug intended for the treatment of RNA-based viruses, and evaluated for use against the Ebola virus, but Remdesivir had not yet received FDA approval for an indication prior to its authorization as a COVID-19 treatment.

Conclusion

Drug repurposing is a powerful tool for future medicine

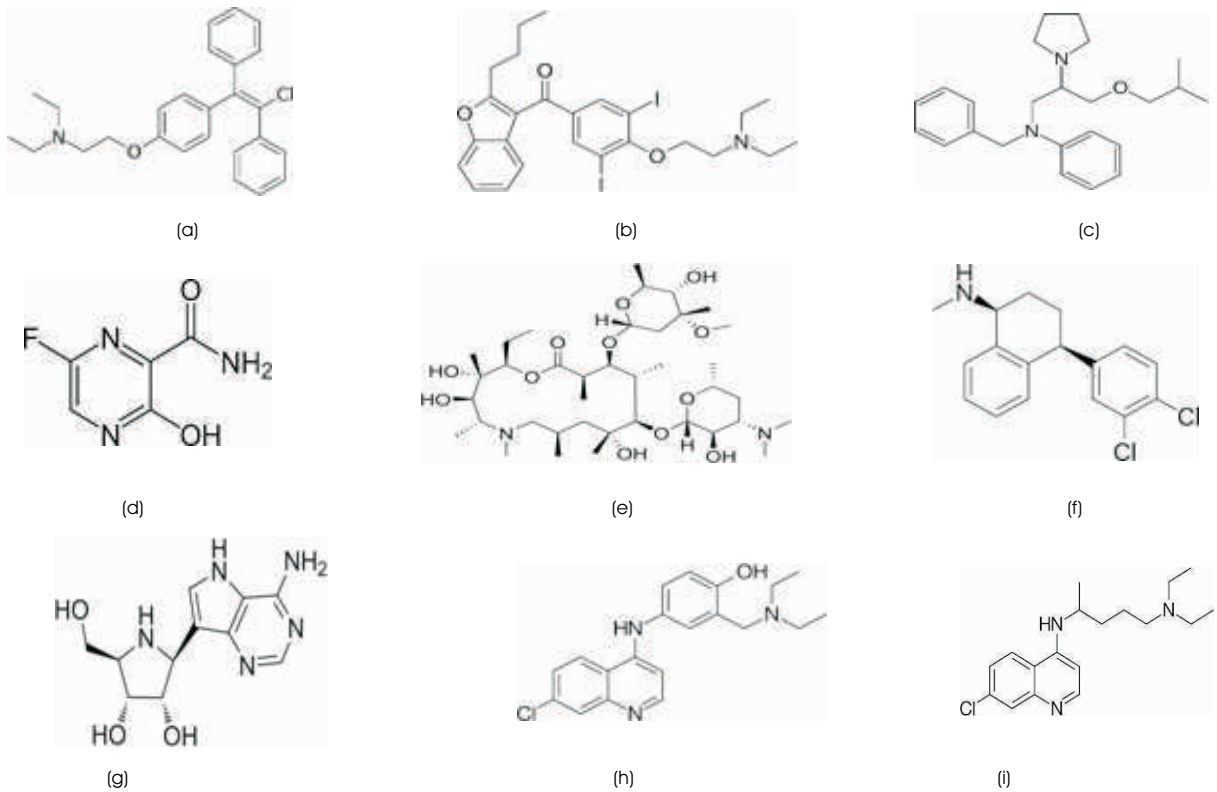

Figure 8. Drugs Repurposed For Ebola Infections (a) Clomiphene, (b) Aamiodarone, (c) Bepridil, (d) Favipiravir, (e) Azithromycin, (f) Sertraline, (g) Galidesivir, (h) Amodiaquine, (i) Chloroquine

through this process of discovering new uses for existing drugs. It offers a promising and cost-effective approach to address unmet medical needs. Drug repurposing drastically cuts the time and expense involved in developing new medications by utilizing safety profiles and efficacy data that are currently available. In a diverse population of humans, everyone has unique sets of inherited or non-inherited genetic abnormalities that result in certain individuals responding less or not to all general treatments or drugs. Medicines that have been approved may not be suitable for a person because of the deficiency of a specific target. Therapeutic efficacies vary significantly across gene profiles due to the variability of human diseases. This situation leads to the requirement of personalized medicines. Reduced lack of efficacy drug repurposing approach has a significant role; this results in best medicine accompanied by low toxicity and high efficacy. This is achieved together with the advancement of next-generation sequencing technologies; personalized genomic studies can be conducted with an affirmative approach. Drug repurposing is exciting and fast-developing and possesses the potential to completely change the pharmaceutical industry's approach to the development of medications.

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