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Review

# Drug Repositioning in Response to COVID-19 and other Challenging Diseases

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**Abstract:** Coronavirus disease is a highly contagious infection that is majorly associated with upper respiratory tract illnesses. The World Health Organization (WHO) label the novel coronavirus disease COVID-19 after an epidemic of the disease in Wuhan, Hubei province (China). Over 90 clinical trials, including drug repositioning, have been initiated to get COVID-19 treatment/management. Antibiotic resistance, drug tolerance, mutation, and adverse drug effects possess a lot of setbacks during therapy, especially with emerging infectious diseases. This necessitates the need for research into getting newer drugs or repositioning the available ones to meet up with the treatment of both infectious and non-infectious diseases affecting humanity. Drug repositioning is a stepwise process that aids in discovering new indications and therapeutic targets of drugs and it usually takes 3-12 years on average to be completed whereas, in drug discovery, an average of 10-17 years is needed for the whole process. This is because, in repositioning, the research process goes straight to preclinical and clinical trials since both the toxicological and pharmacological profiles of the drug to be repositioned are known, thus reducing time, risk, and costs. Based on 2009 statistics, 30% of all drugs sold in that year are products of repositioning while only one out of one million potential drug candidates have the possibility of entry into clinical studies with a tendency of significant failures. Hence the need to discover additional uses for already established drugs, especially with the emergence of COVID-19. Drug repositioning is therefore considered an alternative way to new drug development as it entails the discovery of newer therapeutic uses of established drugs.

**Keywords:** Drug Repositioning, New Drug Discovery, Approaches to Drug Repositioning, Repositioned Drugs, COVID-19

## Introduction

The world became chaotic when the World Health Organisation (WHO) was notified in 2019 that an outbreak of a pneumonia-like disease in Wuhan, Hubei province China, and the etiology was found to be coronavirus (WHO, 2019). The virus belongs to the genus *Betacoronavirus*. It is an enveloped RNA virus that generally affects animals, birds, man, and other mammals. Coronavirus infection is primarily associated with mild to moderate upper respiratory illnesses (Fehr and Perlman, 2015). The World Health Organisation called this new coronavirus infection COVID-19 with documented confirmed cases in more than 110 countries of the world (WHO, 2019; Perrella *et al*., 2020). There exist more than five different species of the virus found to affect humanity, some of the species that are found to cause common cold symptoms include 229E, OC43, NL63, and

HKU1 (Zhu *et al*., 2020). The treatment, management, prevention, and control of COVID-19 is a global issue because of viral mutation and the availability of different strains of the virus. Currently, are no drugs approved for the treatment or management of the coronavirus infection (Li and De Clercq, 2020), however, there are over 80 clinical trials including drug repositioning that have been initiated to get COVID-19 treatment as captured in the clinicaltrials.gov database (Maxmen, 2020).

The Discovery of new drugs is complex, expensive, and involves high-risk processes. Findings from Eastern Research Group (Sertkaya *et al*., 2014) reveal that a period of 10-15 years is required in developing a new molecular entity (drug). However, developing a new molecular entity involves a very delicate process that involves a very high capital investment with little expectations of success (Kaitin, 2010; Scannell *et al*., 2012) and as such, new drug discovery only recorded an average success of about 2.01% (Yeu *et al*., 2015). The success of drug discoveries is infinitesimal as there has been a sharp decline in new drug approvals by the Food and Drug Administration since 1995 (FDA, 2018). Hence, it is of paramount importance to divulge time and resources in finding new strategies for discovering additional indications for already established drugs, especially with the emergence of various infectious diseases ravaging the world.

Drug Repurposing or repositioning (DR) is the process of discovering additional indications as well as therapeutic targets for drugs that are established already. Research findings report that drugs usually bind to more than one target protein or may activate different signaling pathways (Paolini *et al*., 2006; Mestres *et al*., 2008). In-depth knowledge of polypharmacology is a prerequisite in DR (Lavecchia and Cerchia, 2016). More than 20% of all drugs including vaccines sold in 2009 are products of drug repositioning which indicates the degree of importance and prospects associated with drug repositioning (Sardana *et al*., 2011; Graul *et al*., 2010).

The traditional research and drug formulation process is broadly categorized into 2 major stages: (i) Preclinical and (ii) clinical trial stages. The first stage which is the preclinical trial stage is mainly focused on the recognition and development of molecules, ascertainment, and affirmation of a certain molecular target, and the consciousness of pharmacological and toxicological aspects through different forms of tests (Lombardino and Lowe, 2004; FDA, 2018). The main objective of this stage borders on acquiring a new drug; a drug with a particular therapeutic action that has never been described in any literature (Branch and Agranat, 2014). The second stage which is the clinical stage is subdivided into 4 distinct phases: The first phase which is like a pilot study is aimed at determining the level of drug tolerance by the people and determining the safest dosage (Brunton *et al*., 2006). Phase II is mainly associated with the evaluation of effectiveness and safety margin during the therapy of a specified ailment or condition which makes it necessary for experimental continuity. Phase III also evaluates toxic effects and safety margin but uses a greater number of sick individuals, preferably having several participants representative of the number of individuals that intended to use the drug in question. A juxtaposition will therefore be done to substantiate the new therapy regimen and the already established treatment (Katzung *et al*., 2011; FDA, 2018). Phase IV, which is the last phase is known as pharmacovigilance and at this phase, the drug in question has been accepted for use. The main aim of this stage is a lifelong appraisal of selected variables usually not considered during the past phases. Some of the variables or parameters include aftereffects, complications, incompatibility, and drug interactions (Brunton *et al*., 2006; FDA, 2018).

## *Drug Repositioning; Advantages and Challenges*

Drug repositioning is considered a better alternative to new drug development because most already established drugs possess the following pharmacological parameters:

1. Already accepted and documented formulary and production processes
2. Established pharmacodynamics data
3. Documented and passed positive results of clinical trials and safety-margin data (Ashburn and Thor, 2004) and
4. Safe pharmacovigilance data obtained through post-marketing surveillance (Tobinick, 2009)

According to statistics, there are about 49 already established and approved drugs that have been successfully repositioned to manage other conditions different from the initial ones for which the drug was initially developed to manage (Ashburn and Thor, 2004; Chong and Sullivan, 2007; Padhy and Gupta, 2011).

Repositioning when compared with traditional approaches to drug development can be said to have several advantages. In drug repositioning, the process starts from preclinical testing and clinical trials so therefore, the 9-10 years used at the initial stage of new drug development is no longer needed, thus reducing time, risk, and costs. A variety of parameters such as pharmacological, toxicological, and other safety information are known before the start of a repositioning process as the drug that is to be repositioned has already passed through the required drug development stages which include but are not restricted to structural optimization, preclinical and clinical trials (Ashburn and Thor, 2004; Padhy and Gupta, 2011; Oprea and Mestres, 2012; Novac, 2013; Zheng *et al*., 2018). Juxtaposing new drug development with drug repositioning, a remarkable reduction in the duration of time exhausted during research and development can be noticed. In new drug development, about 10 to 17 years are completely exhausted on research and development, whereas in drug repositioning, it takes 3 to 12 years to reposition a drug (Zheng *et al*., 2018; Vora *et al*., 2016) as shown in Tables 1 and 2.

**Table 1:** Timeline of Traditional Approach to Drug Development

| Traditional approaches to drug development (10-17 years) | Target discovery (2-3 years) | Discovery and screening (0.5-1 year) | Lead optimization (1-3 years) | ADMET (1-2 years) | Development (1-6 years) | Registration (1-2 years) | Market entry |
|---|---|---|---|---|---|---|---|
| Little probability of success | Expression analysis, In vitro function, In vivo validation, bioinformatics | Discovery (traditional, combinatorial chemistry, structure-based drug design. Screening (in vitro, Ex, and in vivo HTS/HCS | Traditional, medicinal, chemistry; rational drug design | Bioavailability and systemic exposure (absorption, clearance and distribution) | Must start clinical testing at phase I | USA (FDA), Europe (EMEA), Japan (MHLW) and Brazil (ANVISA). Nigeria (NAFDAC), the Rest of the world | |

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity
HTS/HCS: High-Throughput Screening/High-Content Screening
FDA: Food and Drug Administration
EMEA: European Medicines Evaluation Agency
MHLW: Ministry of Health, Labor and Welfare
ANVISA: Agencia Nacional de Vigilancia Sanitaria
NAFDAC: National Agency for Food and Drug Administration and Control

**Table 2:** Timeline of drug repositioning

| Drug repositioning (3-12 years) | Compound (1-2 years) | Compound acquisition (0-2 years) | Development (1-6 years) | Registration (1-2 years) | Market entry |
|---|---|---|---|---|---|
| Reduced safety and pharmacokinetic uncertainty | Targeted searches, novel insights, specialized screening platforms, serendipity | Licensing, novel Intellectual Property (IP), both licensing novel IP, internal sources | May start at the preclinical, phase I, or phase II stages, ability to leverage existing data packages | USA (FDA), Europe (EMEA), Japan (MHLW) and Brazil (ANVISA). Nigeria (NAFDAC), the Rest of the world | |

However, drug repositioning faces several challenges which include the need for additional clinical/preclinical studies in a situation whereby the available data is outdated or does not meet the standards enshrined in the National Health Surveillance Agency (ANVISA), Food and Drug Administration (FDA) or the European Medicines Agency (Ashburn and Thor, 2004; Padhy and Gupta, 2011). Another glaring holdback is the issue of reduced efficacy and narrow safety margin of the drug to be repositioned in respect of the new indication, as the initially approved dosage of the drug under repositioning will either be below or above the new therapeutic dosage. Many pharmaceutical companies that specialize in DR are often faced with the problems of inadequate skilled personnel, technical know-how, and trade uncertainties. A typical example of successful repositioning is the case of mifepristone, which was repositioned to manage hyperglycemia which is as a result of hypercortisolism in aged individuals that are suffering from type-2 diabetes mellitus by "Corcept Therapeutics" which is an organization that is highly concerned with repositioning (Fleseriu and Petersenn, 2012; Novac, 2013). The success of drug repositioning can be increased using different drug combinations with a similar or different mechanism of action but working synergistically (Sun *et al*., 2016; Zheng *et al*., 2018).

## *Classification of Drug Repositioning*

Drug repositioning may be classified based on the drug targets or based on the type of approaches used in repositioning the drug (systemic or accidental approach).

Classification based on target could be on target repositioning which entails the finding of additional uses of a drug using its already established mechanism of action and non-target repositioning which involves the determination of additional uses of a drug by examining its chemical and target structure. This is seen in the determination of the anti-tuberculosis effect of the drug entacapone (originally an anti-Parkinson drug) and the determination of the anti-HIV properties of the drug haloperidol. Classification could also be based on the kind of approach employed during the repositioning process: New drug indications can be accidentally discovered during research that is not within the scope of repositioning. Below are some examples of accidental repositioning (Razieh *et al*., 2018):

1. Serendipitously as in the case of thalidomide
2. Target dependent just like in the case of everolimus
3. Pathway dependent just as in the case of duloxetine
4. Based on adverse effects like in the case of sildenafil

The systemic approach is the discovery of additional uses of the already established drug through scientific research. Two major criteria have been identified in the

systemic approach which includes experimental and Insilico approaches (Loging *et al*., 2011).

The Experimental approach aims at discovering a new drug or repositioning an already established drug to determine its additional uses. The repositioning has a great deal of experimental and economic advantage because the pharmacokinetic and pharmacodynamic properties of the drug in question are already determined and documented. The approaches used in experimental screening can be target-focused or phenotype screening approaches. Target-focused screening approach entails the evaluation of a drug and its mechanism of action while the Phenotype screening approach deals with the screening and evaluation of a disease and its pathophysiology. The phenotypic approach is usually more reliable than the target-focused approach, this is because pathways for signaling are usually not always examined in the target-focused approach whereas, in the phenotypic approach, pathways for signaling are considered and examined.

The Insilico approach uses several designs in collecting and analyzing systemic data. Bioinformatic and chemoinformatic analysis are mostly employed to achieve specific drug repositioning. The Insilico approach is composed of 3 interconnected stepwise approaches that include the aims and objectives, common strategies employed, and resource maintenance (Loging *et al*., 2011).

### *Successfully Repositioned Drugs*

Drug repositioning has recorded considerable success, some of which are listed in Tables 3 and 4 (Li and Jones, 2012) (Gupta *et al*., 2013).

### *COVID-19 and Drug Repositioning*

COVID-19 is a highly infectious and contagious infection that was formally announced as a pandemic by the World Health Organization in early 2020 (Zawilska *et al*., 2021). Infection is associated with a significant viral amplification leading to the manifestation of mild to moderate symptoms that may later progress to acute symptoms which are primarily due to inflammatory cytokine and inflammatory cell infiltration causing severe lung damage, thrombosis, wet lung and dyspnea (Zawilska *et al*., 2021). The end stage of the disease usually results in death (Zawilska *et al*., 2021). Currently, there is no approved, definite therapy by the FDA. However, there are many drug candidates in the process of being repositioned to discover whether they have activities against COVID-19 apart from their already approved indications. There are over one thousand registered international research on ClinicalTrials.gov (PRMA, 2015). Various medications that possess both antiviral and anti-inflammatory activities have been recommended for repositioning for COVID-19 management (Stebbing *et al*., 2020). Some antimalarial agents with both anti-inflammatory and immunomodulatory properties like chloroquine and hydroxychloroquine have been found to possess inhibitory activities for SARS-CoV-2, SARS-CoV-1, and MERS-CoV (Sanders *et al*., 2020). Experiments to determine the potential potency of chloroquine and hydroxychloroquine on COVID-19 reveal positive *in vitro* results. However, there are very limited documented clinical data. Even though investigations at the clinical level are ongoing to determine the authenticity and reliability of the *in vitro* positive results obtained, Azithromycin which belongs to the macrolide class of antibiotics was found to successfully potentiate the activity of hydroxychloroquine in COVID-19 management, hence its continuous recommendation in COVID-19 complementary management and therapy (Gautret *et al*., 2020). The use of lopinavir together with ritonavir (CYP3A4 inhibitor) as a combination therapy against COVID-19 has been found to possess positive results in preclinical studies since the combination was found to obstruct the chief protease of SARS-CoV-1 and hinders viral replication (Ratia *et al*., 2008), however, similar research couldn't authenticate this result (Cao *et al*., 2020). Already repositioned and FDA-certified medications for the management of COVID-19 are presented in Table 5 (Rodrigues *et al*., 2022) while some selected drugs under the repositioning process for COVID-19 treatment with their current phase of clinical trials are listed in Table 6 below as extracted from ClinicalTrials.gov (PRMA, 2015).

### *Contemporary Ways of Finding Drug Candidates for Repositioning*

Determining new targets for existing drugs is paramount in drug repositioning and the likelihood of finding a distinct and multiple target drug is fascinating even though the processes involved are highly complex. At the initial stage, all drugs to be repositioned should be thoroughly examined and checked for multiple targets and must achieve a particular combination of target harmony. There are 2 major ways of finding drug candidates for repositioning.

Experimental approach: This has been divided into 3 categories:

- The first category is aimed at determining the immediate binding associates of already approved drugs (Brehmer *et al*., 2005)
- A second category is a cell-based approach that screens drugs known to elicit the needed response. They are usually applied in the search for already-certified drugs that control autophagy, a process of reusing damaged cells (Zhang *et al*., 2007). They can also be used to initiate cell death as seen in apoptosis (Antczak *et al*., 2009), or hinder the growth of prostate tumor cells (Iljin *et al*., 2009)
- The third category employs the concept of gene expression analysis in selecting drug candidates which possess a contrasting gene expression outline

ta a disease under study (Lamb *et al*., 2006) or that which poses a related gene expression profile to other licensed drugs (Iorio *et al*., 2010)

- The experimental approach in drug repositioning is faced with the challenges of assembling certified drugs though some companies have been selling pamphlets that contain few approved or off-patent drugs. In recent times, the National Institute of Health's Chemical Genomics Centre compiled a database of pharmaceutical collection with over two thousand lists of certified and licensed drugs (Huang *et al*., 2011). Apart from the approved drugs, all the drug candidates that couldn't scale through the advanced stages of clinical studies only because of low potency/efficacy and not toxicity constitute a great deal of resourceful knowledge for repositioning because the clinical and pharmacokinetic data of the compounds have been established (Broder, 2010)

Computational approaches: There are many established computational methods for drug repositioning. The best way to classify the available methods is through categorization based on drugs or diseases. The Drug-based approach might be preferred if there is a proper understanding and adequate knowledge of the pharmacological properties of the drug to be repositioned. The Disease-based approach can be adopted when the pharmacological profile of the drug is not available. Incorporating components that are drug and disease-related is key to achieving a meaningful and long-lasting repositioning process (Dudley *et al*., 2011).

Most drug-based approaches are centered on the analogy linking target protein, drug, and adverse effect phenotypes (Keiser *et al*., 2009; Kinnings *et al*., 2009; Campillos *et al*., 2008). These approaches presume that drugs with related targets are likely to have closely related chemical structures or adverse effects. Molecular docking, a higher-resolution method has been universally employed in evaluating huge chemical libraries to determine the target of interest. Inverse docking was proposed in the year 2001 to probe the docking of a drug against many proteins binding sites (Chen and Zhi, 2001). Thereafter, other approaches were approved to study numerous targets and drugs (Yang *et al*., 2010; Li *et al*., 2006; Li *et al*., 2010; Li *et al*., 2011).

**Table 3:** Some repositioned drugs, their targets, and indications

| Drug name | Original target | Original indication | New target | New Indication |
|---|---|---|---|---|
| Duloxetine | Serotonin and norepinephrine reuptake | Depression | Serotonin and | Stress, urinary incontinence, fibromyalgia, chronic musculoskeletal pain |
| Everolimus | mTOR | Immunosuppressant | Unchanged | Pancreatic neuroendocrine tumors |
| Imatinib | BCR-ABL | CML | KIT, PDGFRA | GIST |
| Minoxidil | Unknown | Hypertension | Unknown | Hair loss |
| Nelfinavir | HIV-1 protease | AIDS | Inhibits AKT pathway | In clinical trials for multiple cancers |
| Sildenafil | PDE5 | Angina | Unchanged | Erectile dysfunction, pulmonary arterial hypertension |
| Sunitinib | Multiple kinases | GIST, renal cell carcinoma | | Unchanged Pancreatic neuroendocrine tumors |
| Trastuzumab | HER2 | HER2-positive breast cancer | | Unchanged HER2-HER2-positive metastatic gastric cancer |
| Crizotinib | MET kinase | Clinical trials for anaplastic large-cell lymphoma | EML4-ALK oncogene | NSCLC |
| Thalidomide | Unknown | Morning sickness (withdrawn) | Inhibits tumor necrosis factor α production | Leprosy |
| Thalidomide | Unknown | Morning sickness (withdrawn) | Inhibits angiogenesis | Multiple myeloma |
| Zidovudine | Reverse transcriptase | Failed clinical trials for cancer | Reverse transcriptase | AIDS |
| Bevacizumab | VEGF | Multiple cancers | Unchanged | Failed clinical trial for gastric cancer |
| Buproprion | Unknown | Depression | Synergistic inhibition of appetite and energy, expenditure | Obesity (rejected by FDA owing to adverse effects) |
| Naltrexone | Opioid receptors | Opioid addiction | Obesity (rejected by FDA owing to adverse effects | Obesity (rejected by FDA owing to adverse effects) |
| Sunitinib | Multiple kinases | GIST, renal cell carcinoma | Multiple kinases | Failed clinical trials for multiple cancers |

**Table 4:** Drugs repositioned for anticancer treatment

| Drug | Original indication | New anticancer indication |
|---|---|---|
| Thalidomide | Antiemetic in pregnancy (TNF-a↓) | Multiple myeloma (NF-KB↓, STAT3↓) |
| Aspirin | Analgesic, antipyretic (COX-1↓, COX-2↓) | Colorectal cancer (COX-2↓, NF-KB↓, AP-1↓) |
| Valproic acid | Antiepileptic (GABA↑) | Leukemia, solid tumors (HDACI↓, HDACII↓, NF-KB↓, IL-6↓) |
| Celecoxib | Osteoarthritis, rheumatoid arthritis (COX-2↓) | Colorectal cancer, lung cancer (COX-2↓, NF-KB↓) |
| Metformin | Diabetes mellitus (AMPK↑) | Breast, adenocarcinoma, prostate, and colorectal cancers (AMPK↑, NF-KB↓, TNF↓, MCP-1↓) |
| Rapamycin | Immunosuppressant (mTOR↓) | Colorectal cancer lymphoma, leukemia (NF-KB↓, IL-6↓, IKK↓) |
| Methotrexate | Acute leukemia (DHFR↓) | Osteosarcoma, breast cancer, Hodgkin lymphoma (NF-KB↓, TNF-a↓) |
| Zoledronic acid | Anti-bone resorption (osteoclast↓) | Myeloma, prostate cancer, breast cancer (CXCR-4↓, MMPs↓, IL-6↓, Bcl-2↓, Bax↑, FOXO3a↑) |
| Wortmannin | Antifungal | Leukemia (NF-KB↓, AP-1↓) |
| Minocycline | Acne | Ovarian cancer, glioma (MMPs↓) |
| Thiocolchicoside | Muscle relaxant (GABA↓) | Leukemia, multiple myeloma (NF-KB↓) |
| Nitroxoline | Antibiotic | Bladder, breast cancers (MetAP-2↓) |

**Table 5:** Drugs repositioned for COVID-19 treatment

| Drug | Original indication | Likely mechanism of action against COVID-19 |
|---|---|---|
| Baricitinib | Rheumatoid arthritis | Modulates cytokine production |
| Chloroquine and Hydroxychloroquine | Malaria, chronic inflammatory diseases | Prevents virus entry and decapsidation. Also Modulates the host immune system |
| Dexamethasone | Inflammatory conditions (e.g., bronchial asthma, endocrine and rheumatic disorders) | Bind to the cellular glucocorticoid receptor, modulates the production of pro-inflammatory and anti-inflammatory signals |
| Favipiravir | Influenza virus | Inhibits virus RNA synthesis |
| Ivermectin | Anti-parasitic. Intestinal strongyloidiasis and onchocerciasis, pediculosis and rosacea | Inhibits the cellular importin α/β-mediated nuclear transport of proteins |
| Lopinavir-Ritonavir | HIV/AIDS | Inhibits the virus 3CL protease |
| Masitinib | for Cancer, and asthma, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis. | Inhibits the virus 3CL protease |
| Molnupiravir | Influenza viruses and encephalitic alphaviruses | Inhibits virus RNA synthesis |
| Remdesivir | Ebola virus | Inhibits virus RNA synthesis |
| Tocilizumab | Rheumatoid arthritis and other autoimmune rheumatic diseases | Inhibits IL-6 activity |
| Umifenovir | Influenza and others respiratory viruses. | Blocks virus attachment and entry. Also Modulates immune response and interferon production |

**Table 6:** Ongoing drug repositionings for COVID-19 treatment

| Drug | Clinical condition | Clinical trial stage |
|---|---|---|
| Hydroxychloroquine | 30 participants with pneumonia caused by 2019-nCoV | Phase 4 |
| Chloroquine | 10000 participants in a prophylaxis study for COVID-19 | Phase 4 |
| Human immunoglobulin | Pneumonia caused by 2019-nCoV with 80 participants | Phases 2 and 3 |
| Remdesivir | Severe respiratory infection caused by 2019-nCoV with 452 participants | Phase 4 |
| Remdesivir | 308 participants with mild/moderate respiratory infection caused by 2019-nCoV | Phase 4 |
| Arbidol (umifenovir) | Pneumonia caused by 2019-nCoV with 380 participants | Phase 4 |
| Arbidol or lopinavir-ritonavir or oseltamivir | 400 participants infected with 2019-nCoV | Phase 4 |
| Arbidol or lopinavir-ritonavir | 125 participants infected with 2019-nCoV | Phase 4 |
| Darunavir-cobicistat combination | Pneumonia caused by 2019-nCoV with 30 participants | Phase 3 |
| TCM combination with lopinavir-ritonavir, a-interferon via aerosol | 150 participants infected with 2019-nCoV | Phase 4 |
| Recombinant human interferon a2b | 328 participants with COVID-19 | Phase 1 |
| Carrimycin or lopinavir-ritonavir or arbidol or chloroquine phosphate | 520 participants with COVID-19 | Phase 4 |
| Danoprevir-ritonavir and interferon | | |

**Table 6:** Continue

| | | |
|---|---|---|
| inhalation or lopinavir-ritonavir or | 50 participants with pneumonia caused by 2019-nCoV | Phase 4 |
| Xiyanping or lopinavir-ritonavir interferon inhalation | 384 participants with pneumonia caused by 2019-nCoV | N/A |
| Xiyanping combined lopinavir-ritonavir | 80 participants with COVID-19 | N/A |
| Combinations of oseltamivir, favipiravir and chloroquine | 80 participants with COVID-19 | Phase 3 |
| Thalidomide | 40 participants with COVID-19 | Phase 2 |
| Thalidomide | 100 participants with pneumonia caused by 2019-nCoV | Phase 2 |
| Vitamin C | 140 participants with severe pneumonia caused by 2019-nCoV | Phase 2 |
| Methylprednisolone | 80 participants infected with 2019-nCoV | Phase 2 |
| Pirfenidone | 294 participants with severe pneumonia caused by 2019-nCoV | Phase 3 |
| Bromhexine hydrochloride | 60 participants with suspected and mild pneumonia caused by 2019-nCoV | N/A |
| Bevacizumab | 20 participants with severe COVID-19 pneumonia | Phases 2 and 3 |
| Fingolimod | 30 participants with COVID-19 | Phase 2 |

The application of computational approaches in the analysis of data available in accredited databases like the PubChem Bioassays (Chen *et al*., 2009) and Gene Expression Omnibus has been on the increase (Dudley *et al*., 2011). Recently discovered target disease syndicates can be formulated with the help of systems biology methods (Pujol *et al*., 2010). Essential resources used in computational approaches are usually datasets of familiar and well-known interconnections that are frequently employed in training analysis. Other accredited databases containing licensed drugs include but are not restricted to Drug Bank and Matador (Wishart *et al*., 2006; Kanehisa *et al*., 2006; Günther *et al*., 2007; Dudley *et al*., 2011).

### *Failed Repositioning Cases*

Repositioning cases are usually faced with challenges owing to the delicate and technical nature of the process. Sometimes the failure could be because of the inability or failure to take cognizance of the initial indications before designing the repositioning process. Considering a cytotoxic agent for managing mild hypertension could fail due to high toxicity because the repositioned dosage will cause cell damage. A drug called bevacizumab that has been repositioned to manage several cancers surprisingly failed in phase III clinical trials when it was repositioned to manage gastric cancer (Kang and Kauh, 2011). Combination therapy using lopinavir and ritonavir in the treatment of COVID-19 in 2008 preclinical studies later failed clinical trials in 2020 (Cao *et al*., 2020).

The use of bupropion and naltrexone in combination initially licensed by the FDA for the management of depression and opioid addiction appeared to also work in synergism to control hunger and vigor consumption in obesity (Plodkowski *et al*., 2009). However, through pharmacovigilance, the combination was later deregistered by the FDA because of its potential cardiovascular side effects (Caveney *et al*., 2011).

Pharmacovigilance which is the practice of monitoring the effects of drugs after they have been licensed for use by the public to identify and evaluate previously unreported adverse effects or reactions is key in the drug repositioning process.

## Conclusion

Drug repositioning is not only cheaper but safer in the search for agents to meet the challenges of already existing and emerging diseases like COVID-19. Given the high cost, complexity, time, and risk associated with developing a new molecular entity (new drug), a possible, efficient, and cost-effective alternative is to reposition the existing drugs to target disease conditions different from their initial indication. The drug candidates are licensed and approved by the regulatory agencies concerned and therefore, such drugs can easily be repositioned since both the pharmacological and toxicological profiles of the drugs are known and documented. Additionally, already licensed drugs have been duly linked with their target proteins which could be of help during repositioning especially when the target has been established to be applicable in other disease conditions that have a common target. However, inhibiting the original target might result in adverse allergic effects in off-target's associated diseases. It is therefore recommended that proper enlightenment programs and symposiums on drug repositioning should be intensified and scientific research on drug repositioning should be encouraged to cover all the aspects involved in drug repositioning since the strategy of repositioning is safer and financially appealing when juxtaposed with the financial implications involved in new drug development.

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## Author's Contributions

**Hyellavala Joseph Fomnya and Saidu Ibrahim Ngulde:** Conceptualization, study design, manuscript writing.

**Sarah Malgwi Gana and Garleya Bilbonga:** Data acquisition and analysis.

**Kazabu Ahmed Amshi, Chahari Alfred Midala and Kabiru Alhaji Garba:** Critical review and analysis of the manuscript.

## Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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