Chapter

Drug Repurposing (DR): An Emerging Approach in Drug Discovery

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Abstract

Drug repurposing (DR) (also known as drug repositioning) is a process of identifying new therapeutic use(s) for old/existing/available drugs. It is an effective strategy in discovering or developing drug molecules with new pharmacological/therapeutic indications. In recent years, many pharmaceutical companies are developing new drugs with the discovery of novel biological targets by applying the drug repositioning strategy in drug discovery and development program. This strategy is highly efficient, time saving, low-cost and minimum risk of failure. It maximizes the therapeutic value of a drug and consequently increases the success rate. Thus, drug repositioning is an effective alternative approach to traditional drug discovery process. Finding new molecular entities (NME) by traditional or *de novo* approach of drug discovery is a lengthy, time consuming and expensive venture. Drug repositioning utilizes the combined efforts of activity-based or experimental and *in silico*-based or computational approaches to develop/identify the new uses of drug molecules on a rational basis. It is, therefore, believed to be an emerging strategy where existing medicines, having already been tested safe in humans, are redirected based on a valid target molecule to combat particularly, rare, difficult-to-treat diseases and neglected diseases.

Keywords: drug repurposing, drug discovery, *in silico* repositioning, activity-based repositioning, target-based screening, therapeutic indication

1. Introduction

Drug repurposing (DR) is also known as drug repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching. It can be defined as a process of identification of new pharmacological indications from old/existing/failed/investigational/already marketed/FDA approved drugs/pro-drugs, and the application of the newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use. It involves establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs [1–3]. Traditional drug discovery is a time-consuming, laborious, highly expensive and high risk process. The novel approach of drug repositioning has the potential to be employed over traditional drug discovery program by mitigating the high monetary cost, longer duration of development and increased risk of failure. It confers reduced risk of failure where a

failure rate of ~45% is associated due to safety or toxicity issues in traditional drug discovery program with additional benefit of saving up to 5–7 years in average drug development time [4, 5]. In recent years, the drug repositioning strategy has gained considerable momentum with about one-third of the new drug approvals correspond to repurposed drugs which currently generate around 25% of the annual revenue for the pharmaceutical industry [6]. It has been accounted that approximately 30% of the US Food and Drug Administration (FDA) approved drugs and biologics (vaccines) are repositioned drugs. According to recent estimates, pharmaceutical industries have significantly placed the market for repurposed drugs at $24.4 billion in 2015 with projected growth up to $31.3 billion in 2020. The first example of drug repositioning was an accidental discovery/serendipitous observations in the 1920s. After about a century of development, more approaches were developed for accelerating the process of drug repositioning. Some most successful and best-known drugs that have been emerged out of the DR approach are sildenafil, minoxidil, aspirin, valproic acid, methotrexate etc. [7]. For example, sildenafil originally developed for the treatment of hypertension and angina pectoris has currently been used to treat erectile dysfunction.

2. Traditional drug discovery vs. drug repurposing

The traditional approach to drug discovery involves *de novo* identification and of new molecular entities (NME), which include five stages: discovery and preclinical, safety review, clinical research, FDA review, and FDA post-market safety monitoring. It is a time-consuming and costly process with high risk of failure [8]. On the other hand, there are only four stages in drug repositioning, which include compound identification, compound acquisition, development, and FDA post-market safety monitoring [9] (**Figure 1**). With the advancement of bioinformatics/cheminformatics tools and availability of huge biological and structural database, drug repositioning has significantly decreased the time and cost of the drug development with reduction in risk of failure. In recent years, the use of *in silico* techniques along with the application of structure-based drug design (SBDD) and artificial intelligence (AI) technology has further accelerated the drug purposing process [10, 11].

However, the repositioning strategy of using approved therapeutics for new therapeutic indications has demonstrated success particularly through prior serendipitous observations. The discovery of drugs by this approach is certainly advantageous as depicted above over traditional drug discovery program as described below. For example, sildenafil (Viagra), a phosphodiesterase-5 (PDE5) inhibitor initially developed for coronary artery disease (angina) by Pfizer (1985) has been repurposed for the treatment of erectile dysfunction. It potentially reduced the development cost at shorter development time. Metformin (Glucophage), an oral anti-diabetic medication used widely in type 2 diabetes mellitus has been developed as a cancer therapeutic which is currently under phase II/phase III clinical trials [1, 12].

Drug repositioning has several advantages in comparison with traditional approaches to drug discovery. When comparing with traditional drug discovery program, a significant reduction of the time spent in R&D can be observed. In traditional approach, it is estimated that 10–16 years are spent for the development of a new drug, while in DR the estimated time is between 3 and 12 years. It only costs $1.6 billion to develop a new drug using a drug repositioning strategy, while the drug development through traditional strategy costs around $12 billion. Moreover, researchers only need 1–2 years to identify new drug targets and about an average of 8 years to develop a repositioned drug [6, 7]. A repositioned drug does not require the initial 6–9 years typically required for the development of new drugs

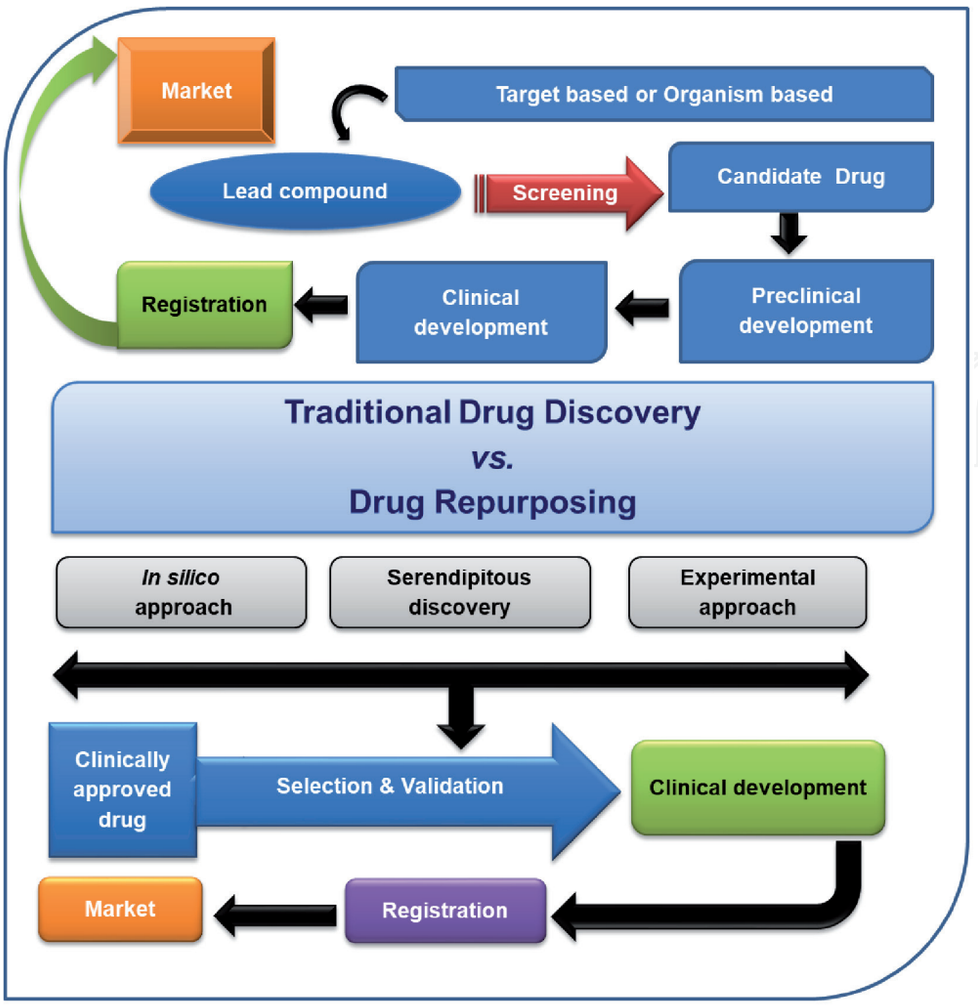

Figure 1.
Traditional drug discovery vs. drug repurposing.

by traditional process, but instead enters directly to preclinical testing and clinical trials, thus reducing the overall risk, time and cost of development. Reports suggest that repurposed drugs require approximately 3–12 years for gaining approval from FDA and/or European Medicines Agency (EMA) and at reduced 50–60% cost. At the beginning of a repositioning project, a range of pre-clinical (pharmacological, toxicological, etc.), and clinical efficacy and safety information is already available, as the candidate drug has already undergone through the early stages of drug development such as structural optimization, preclinical and/or clinical trials, in addition to the possibility of the candidate drug being an approved drug, having its clinical efficacy and safety profile. In this way, there is a reduction of the risks associated with failures in the early stages of development, which are high in traditional approaches, as well as a significant reduction of cost with the possible increase in clinical safety and therefore, high success rate [13, 14].

Due to the availability of previously collected pharmacokinetic, toxicological, clinical and safety data at the start of a repurposing development project, the advantages that are encountered with drug repurposing over traditional drug discovery approach are reduced time of development, lower cost of development and reduced risks of failure in the clinical development.

It has been estimated that the time required for development of a repositioned drug varies from 3 to 12 years (which is about 10–17 years in traditional discovery program) with substantially lower costs, which ensures the repositioning company's significant savings in terms of time and capital. The average cost required to bring

a new drug to market is USD 1.24 billion by traditional drug development process, whereas in drug repurposing it costs around ≤60% expenditure of traditional drug discovery. Some other advantages are as follow. The primary focus of traditional discovery program is to discover drugs to treat chronic and complex diseases, whereas by drug repositioning approach, development of drugs for rapidly emerging and re-emerging infectious diseases, difficult to treat diseases and neglected diseases (NTDs) are focused. Due to the availability of bioinformatics or cheminformatics approaches, huge omics (proteomics, transcriptomics, metabolomics, genomics etc.) data and database resources, disease targeted-based repositioning methods can be used to explore the unknown mechanisms of action (such as unknown targets for drugs, unknown drug–drug similarities, new biomarkers for diseases etc.) of known/existing drugs [13].

3. Strategies of drug repurposing

There are two main strategies of DR, viz., on-target and off-target (**Figure 2**). In on-target DR, the known pharmacological mechanism of a drug molecule is applied to a new therapeutic indication. In this strategy, the biological target of the drug molecule is same, but the disease is different [12].

For example, in the repositioning of minoxidil (*Rogaine*), an on-target profile is observed, since the drug acts on the same target and produces two different therapeutic effects. Minoxidil was transformed from an antihypertensive vasodilator anti hair loss drug. As an antihypertensive vasodilator, minoxidil has the property of widening blood vessels and opening potassium channels, which allows more oxygen, blood, and nutrients to the hair follicles and this pharmacological action helps its use in the treatment of male pattern baldness (androgenic alopecia).

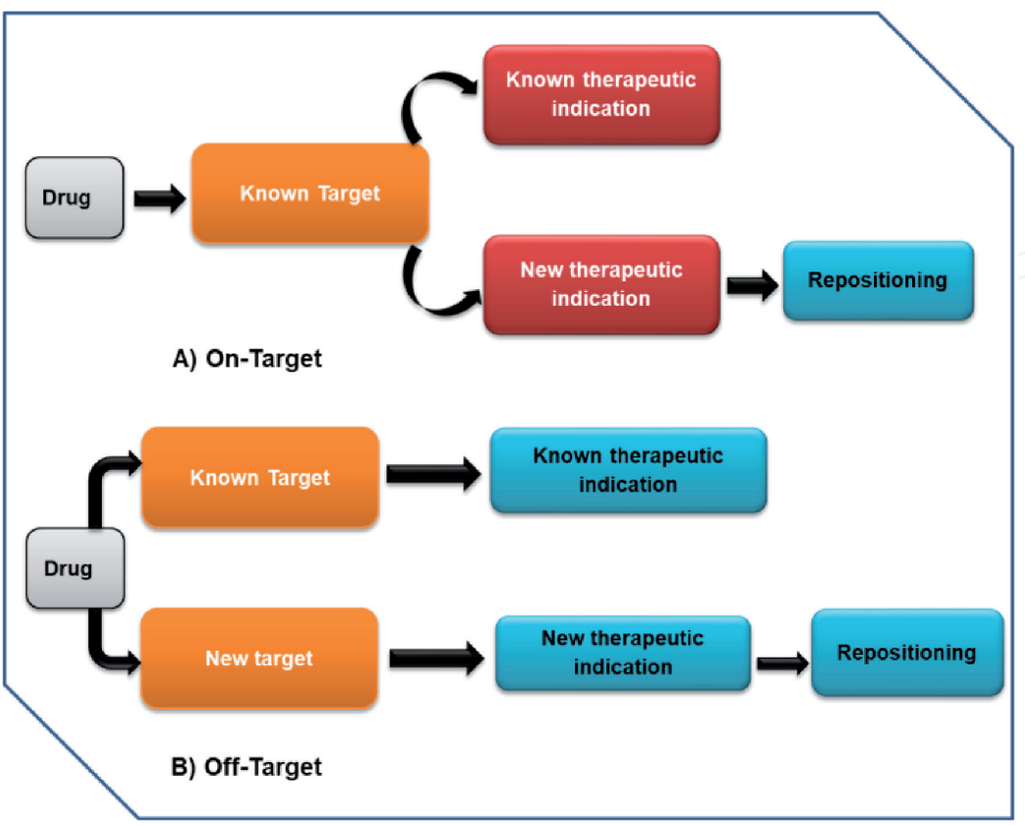

Figure 2.
On-target and off-target strategies of drug repositioning.

On the other hand, in the off-target profile, the pharmacological mechanism is unknown. Drugs and drugs candidates act on new targets, out of the original scope, for new therapeutic indications. Therefore, both the targets and the indications are new [1]. Aspirin (*Colsprin*) is good example of the off-target profile. Aspirin has been traditionally used as NSAID in the treatment of various pain and inflammatory disorders. It also suppresses blood coagulation (clot formation) by inhibiting the normal functioning of platelets (antiplatelet drug). It is, therefore, used in the treatment of heart attacks and strokes. Another new use of aspirin in the treatment of prostate cancer has also been reported.

4. Approaches of drug repurposing

Drug repositioning has two alternative and complementary approaches, one is experiment-based approach and the other is *in silico*-based approach.

The experiment-based approach is also known as activity-based repositioning which refers to the screening of original drugs for new pharmacological indications based on experimental assays. It involves protein target-based and cell/organism-based screens in *in vitro* and/or *in vivo* disease models without requiring any structural information of target proteins. Several approaches of experimental repositioning are target screening approach, cell assay approach, animal model approach and clinical approach [15, 16].

In contrast, *in silico* repositioning carries out virtual screening of public databases of huge drug/chemical libraries using computational biology and bioinformatics/cheminformatics tools. In this approach, the identification of potential bioactive molecules is achieved based upon the molecular interaction between drug molecule and protein target [17].

The differences between activity- and *in silico*-based approaches of drug repositioning are summarized in **Table 1**.

Over the past few decades, the *in silico* approach has gained wide popularity with significant success in drug discovery program. Many pharmaceutical companies and drug discovery research laboratories have already successfully incorporated the *in silico* tools and techniques for the drug discovery from structurally diverse chemical spaces since a large amount of information on the chemical structure bioactive compounds, structure of proteins and pharmacophore models are available in the public domain. Moreover, *in silico* repositioning has some advantages over the experimental-based approach, which includes reduced time and cost of development and low risk of failure. The limitation of this method is that it requires

Activity-based approach	***In silico*-based approach**
Experimental (*in vitro* and *in vivo*) screening	Computational (virtual) screening
Target-based and cell/organism-based screening assay	Protein target-based screening
Requires no structural information of target proteins and drug-induced cell/disease phenotypic information	Requires structural information of target proteins and drug-induced cell/disease phenotypic information
Time and labor consuming	Time and labor efficient
Lower rate of false positive hits during the screening	Higher rate of false positive hits during the screening

Table 1.
Differences between activity- and in silico- *based approaches of drug repositioning [17, 18].*

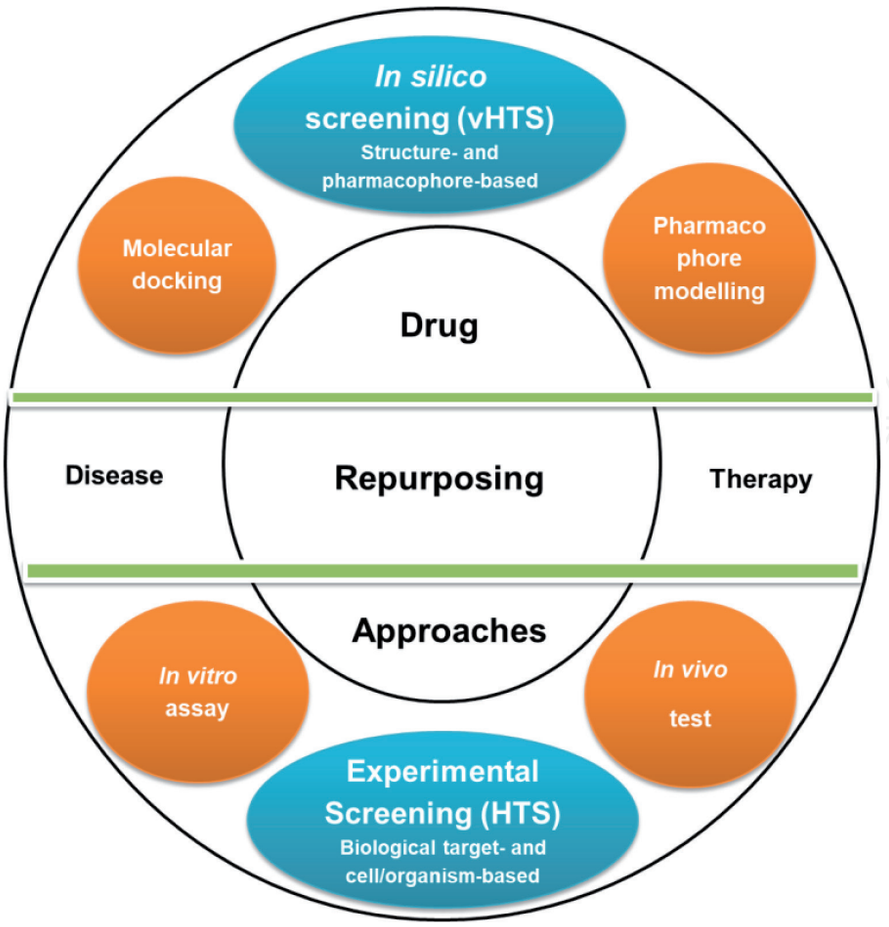

Figure 3.
Approaches of drug repositioning.

precise structural information about drug targets and in case, the protein target is not available, disease specific phenotypic or genotypic profiles of drugs are required [19]. **Figure 3** represents the approaches of drug repositioning.

In recent years, discovery scientists and researchers have combined *in silico* and experimental approaches to identify new therapeutic indications for existing drugs, called mixed approach. In the mixed approach, the result of computational methods is validated by pre-clinical biological experiments (*in vitro* and *in vivo* tests) and clinical studies. The simultaneous application of computational and experimental methodologies in a systematic manner offer a robust and logical approach to the discovery of new indications, demonstrating a greater efficiency than the discovery based on serendipity. Further, mixed approach offers opportunities for developing repositioned drugs more effectively and rapidly. This approach is credible and yet, reliable [20].

5. Methodologies of drug repurposing

The methodologies adopted in DR can be divided into three broad groups depending on the quantity and quality of the pharmacological, toxicological and biological activity information available. These are mainly (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented.

In the drug-oriented methodology, the structural characteristics of drug molecules, biological activities, adverse effects and toxicities are evaluated. This strategy is meant for identifying molecules with biological effects based on cell/

animal assays. This type of repositioning methodology is based on traditional pharmacology and drug discovery principles, where studies are usually conducted to determine the biological efficacy of drug molecules without really knowing about the biological targets. Significant successes in DR have been achieved with this orientation profile, through serendipity or clinical observation, such as discoveries with sildenafil [21].

Target-based methodology comprise *in silico* screening or virtual high-throughput screening (vHTS) of drugs or compounds from drug libraries/compound databases such as ligand-based screening or molecular docking followed by *in vitro* and *in vivo* high-throughput and/or high-content screening (HTS/HCS) of drugs against a selective protein molecule or a biomarker of interest. In this method, there is a significant success rate in drug discovery as compared to drug-oriented method, because most biological targets directly represent the disease pathways/mechanisms [22].

The application of disease/therapy-oriented methodology in DR is relevant when there is more information on the disease model is available. In this case, DR can be guided by the disease and/or treatment based upon availability of information given by proteomics (disease specific target proteins), genomics (disease specific genetic data), metabolomics (disease specific metabolic pathways/profile) and phenotypic data (off-target mechanism, pharmacological targets, disease pathways, pathological conditions, adverse and side effects etc.) concerning the disease process. It, therefore, requires construction of specific disease networks, recognizing genetic expression, considering key targets, identifying disease causing protein molecules related to cell and metabolic pathways of interest in the disease model [23].

Figure 4 delineates the methodologies and steps involved in drug repositioning.

Drug-based phenotypic screening and target-based methods account for more than 50% of the FDA approved small drug molecules and biologics. Phenotypic drug screening methods identify drug candidates from small molecule libraries

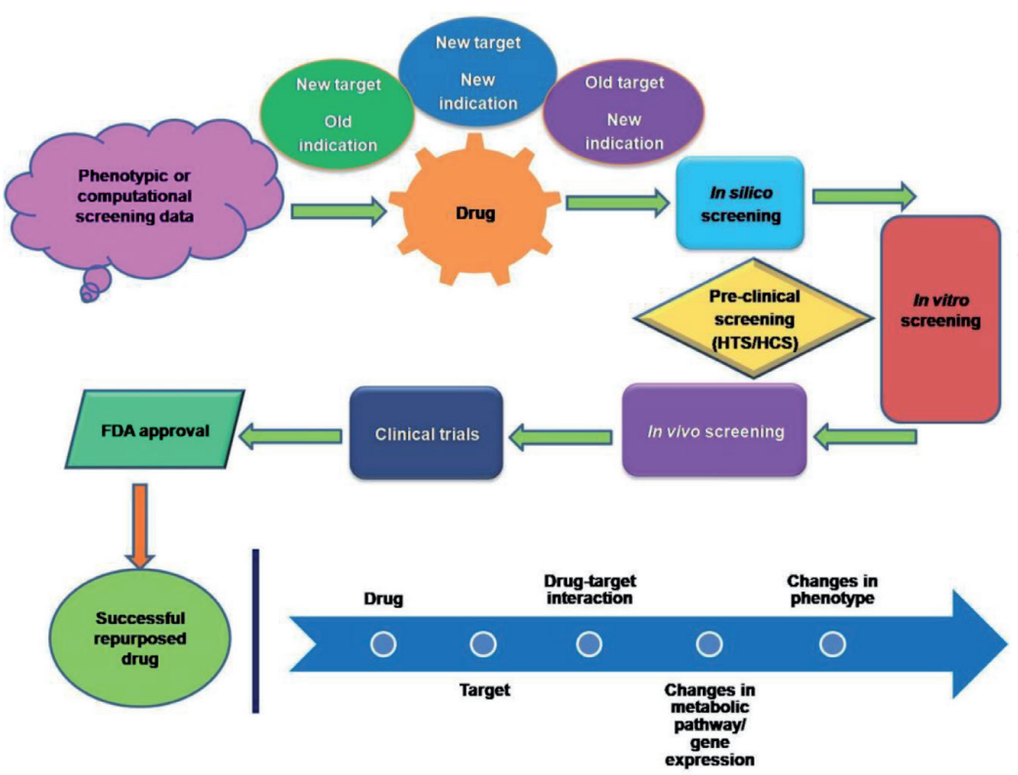

Figure 4.
Methodologies and steps involved in drug repositioning.

by serendipitous observations. Target-based methods discover drugs based upon known target molecules. The treatment/therapy-based repositioning methodology is similar to disease-based methodology [23].

A detailed enumeration of various methodologies employed in drug repositioning along with suitable examples is given in **Table 2**.

Methodology	Type of method, category	Method/specific approach	Example(s)
Drug-oriented			
Phenotypic screening	Blinded/ Target-based, Screening	*In vitro* and *in vivo* HTS/HCS screening	Sildenafil (erectile dysfunction), rituximab (breast cancer)
Target 3D structure, chemical structure, information of drugs and ligands	Target-based, Cheminformatics	*In silico* screening, ligand-based screening and molecular docking, fragment-based screening	Fluorouracil (lung cancer), etoposide (bladder cancer)
Drug-target information, chemical structure, information of targets and drugs	Knowledge-based, Bioinformatics/ Chem-informatics	Drug–target prediction	Simvastatin, ketoconazole (breast cancer)
Clinical trial information and adverse effects	Knowledge-based, Bioinformatics	Drug similarity studies	—
FDA approval labels	Knowledge-based, Bioinformatics	Drug similarity studies	—
Disease-oriented			
Available Pathway information	Knowledge-based, Bioinformatics	Discovery of disease mechanism and address of key targets	Vismodegib (skin cancer)
Disease omics/ genetics data	Signature-based Bioinformatics	Studying gene signatures/ genomics to identify key targets	—
Disease omics data, available pathway information, and protein interaction network	Pathway or network-based, Network biology	Analysis of disease-specific pathways and networks to identify key targets	Sunitinib, dasatinib (breast cancer, brain tumor)
Therapy-oriented			
Drug omics data	Signature- based or Signature- and network-based, Bioinformatics and/or Network biology	Studying gene signatures	Sirolimus (acute lymphoblastic leukemia), Fasudil (neurodegenerative disorders)
Disease omics and drug omics data	Signature based, Bioinformatics	Similarities between drugs and diseases	Cimetidine (lung cancer), topiramate (inflammatory bowel disease)
Drug omics data, disease pathway and protein interaction network	Targeted- mechanism based, Network biology and Systems biology	Elucidating targeted pathways	Daunorubicin, clomifene (breast cancer)

Table 2.
Some available methods of drug repositioning [23, 24].

Several available repositioning methods depicted above in **Table 2** are described briefly as follows:

Blinded search or screening methods involve serendipitous identification from biological tests/experimental screens aimed at specific disease models and drugs. The advantage of these methods is that they possess higher flexibility for screening a large number of drugs or diseases.

Target-based methods carry out *in vitro* and *in vivo* high-throughput and/or high-content screening (HTS/HCS) of drug molecules for a protein target or a biomarker of interest and *in silico* screening of compounds or drugs from large compound libraries, such as ligand-based screening or molecular docking. In these methods, there is a higher possibility of finding useful drugs/drug leads as compared to blinded search methods. It also requires less time for the entire screening process to complete.

Knowledge-based methods utilize bioinformatics or cheminformatics approaches to gather the available information of drug profile, chemical structures of targets and drugs, drug-target networks, clinical trial information including adverse effects, signaling or metabolic pathways. This information content of knowledge-based methods is rich enough as compared to blinded or target-based methods. The known information can be used to predict therefore, be used to predict the unknown new mechanisms, such as unknown targets for drugs, unknown drug–drug similarities, new biomarkers for diseases etc.

Signature-based methods use gene signatures derived from disease omics data (genomics data) with or without treatments to discover unknown off-targets or unknown disease mechanisms. Genomics data are publicly available as databases. The advantage of these methods is that they are useful to explore unknown mechanisms of action of drugs. In comparison to knowledge-based methods, signature-based methods investigate drug mechanisms at more molecular-level, such as changes in expression of genes by using computational approaches.

Pathway- or network-based methods make use of disease omics data, available signaling or metabolic pathways, and protein interaction networks to reconstruct disease-specific path- ways that provide the key targets for repositioned drugs. The advantage of these methods is that they can narrow down general signaling networks from a large number of proteins to a specific network with a few proteins (or target molecules).

Targeted mechanism-based methods integrate treatment omics data, available signaling pathway information and protein interaction networks to describe the unknown mechanisms of action of drugs. The advantage of these methods is that they are not only used to discover the mechanisms related to diseases or drugs, but also to identify those directly related to treatments of drugs to specific diseases [23–25].

6. Repositioned drugs

Drug repositioning is an alternative approach to traditional drug discovery. With increasing market demand many pharmaceutical companies are developing new drugs or new therapeutic uses from existing/old/available drugs by drug repositioning approaches in less time, yet at low cost. In drug discovery program, the repositioning is usually essentially carried out in two stages as described follows. In the first stage, the *in silico* screening of approved drugs against a particular disease target is carried out, which is followed by the second step, in which the selected identified molecules are further experimentally investigated both *in vitro* and *in vivo* in specific disease models of interest. After successful preclinical studies in the

second stage of repositioning, identified drug candidates enter the clinical trials in human subjects [24, 25]. **Figure 5** delineates several potential strategies (with suitable examples) of drug repositioning.

Table 3 depicts examples of some repositioned drugs already developed or currently under development from various approved (FDA) or marketed drugs and investigational new drugs (IND). Some repositioned drugs currently under clinical trials in COVID-19 are also included in the list.

Colchicine, a well-known anti-inflammatory drug used in the treatment of gout and pericarditis, is currently under clinical trial for treating COVID-19 patients. This drug has been proved to be effective in preventing massive cytokine storm induced pneumonia caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). The antiviral effect of an older antimalarial drug, chloroquine (used as phosphate salt) against SARS-CoV-2 infection has also been investigated worldwide. Studies suggest that chloroquine may be beneficial in preventing coronavirus induced pneumonia in COVID-19. As per recent reports from NIH (National Institutes of Health, US), the clinical trial of a combination of hydroxychloroquine/azithromycin for the treatment of COVID-19 patients has already been started. In this combination, both the drugs are FDA approved, where hydroxychloroquine is an antimalarial drug and azithromycin is an antibacterial antibiotic. An anti-viral drug, favipiravir intended for the treatment of influenza is currently under phase-2/phase-3 clinical trials on COVID-19 patients around the world (China, Japan, US, India). Glenmark has initiated phase-3 trial on favipiravir for the treatment of COVID-19 patients in India. An investigational anti-retroviral drug called remdesivir (originally developed by Gilead Sciences Inc. for the treatment of Ebola, but failed in clinical trial) is also under clinical trial for treating COVOD-19 patients in several countries like China, US, UK and India. In India, clinical trials on favipiravir, remdesivir and colchicine are currently underway by CSIR (Council of Scientific & Industrial Research) laboratories. A fixed dose drug combination called lopinavir/ritonavir earlier approved

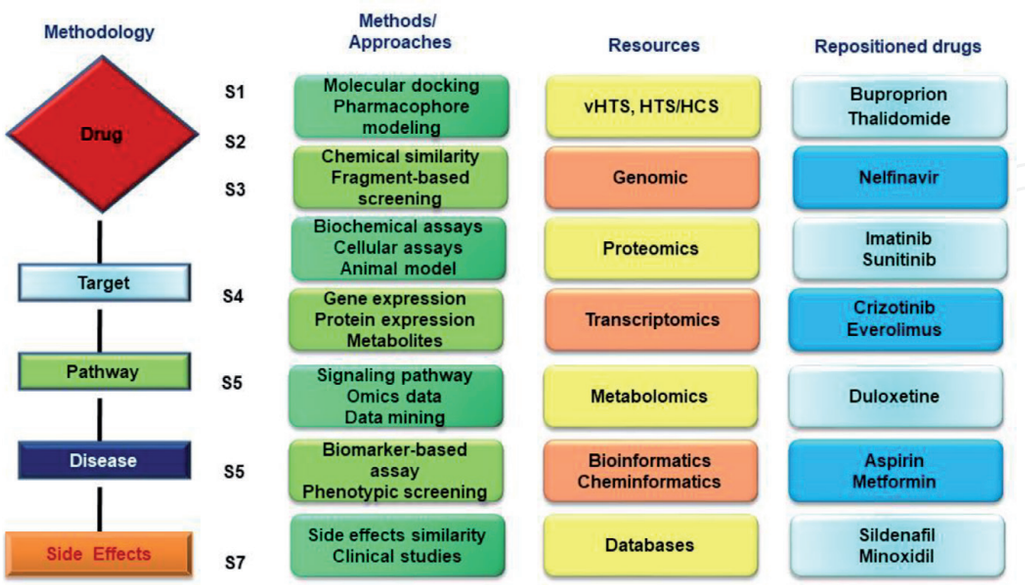

Figure 5.
Strategies of drug repositioning with examples. vHTS: virtual high-throughput screening; HTS/HCS: high-throughput and/or high-content screening; Strategy 1 (S1): serendipitous observation; Strategy 2 (S2): observance of novel activity (specific disease phenotype, rational approach); Strategy 3 (S3): new drug-target interaction; Strategy 4 (S4): new roles for existing protein target; Strategy 5 (S5): new biochemical pathways; Strategy 6 (S6): disease-specific repositioning; Strategy 7 (S7): unexpected side effects.

to treat HIV/AIDS under the brand name *Kaletra* is currently being studied to treat COVID-19 patients in several countries. This drug combination was investigated along with the flu drug, oseltamivir (Tamiflu) to cure infection caused by SARS-CoV-2 in Thailand. The clinical trial of an anti-parasitic drug called ivermectin (used traditionally as an approved treatment in worm infestations) for the treatment of COVID-19 is being undertaken in several parts of the world after a successful *in vitro* effectiveness against SARS-CoV-2 infection at Monash University in Melbourne, Australia. The clinical trial of toclizumab, an IL-6 receptor antagonist (marketed under the brand name *Actemra*) used for the treatment of inflammatory illness such as rheumatoid arthritis is also being conducted for the treatment of patients with COVID-19 [25, 26].

Drug, pharmacological category	Original indication	New indication	Status of development
Amphotericin B (AMB), Anti-fungal antibiotic	Fungal infections	Leishmaniasis	Already developed*
Aspirin, NSAID	Pain and inflammation	CVDs (Anti-platelet)	Already developed*
		Prostate cancer	Under development*
Amantadine, Anti-viral	Influenza	PD	Already developed*
Astemizole, Anti-histaminic	Allergic illness such as urticaria	Malaria	Under development*
Atomoxetine, Anti-depressant	Depression	Attention deficit, Hyperactivity disorder	Already developed*
Avermectin, Anthelmintic	River blindness, Elephantiasis	Tuberculosis	Under development*
Azithromycin, Anti-bacterial antibiotic	Bacterial infections	COVID-19	Under development*
Bromocriptine, Dopamine receptor antagonist	PD	DM (type 2)	Under development*
Bupropion, SSRI, Anti-depressant	Depression	Smoking cessation	Already developed*
Celecoxib, COX-2 inhibitor, NSAID	Inflammation	Breast and colon cancer	Under development*
Chloroquine, Anti-malarial	Malaria	COVID-19	Under development*
Cimetidine, H2 receptor antagonist	Gastric ulcer	Breast, lung and prostate cancer	Under development*
Crizotinib, ALK inhibitor	Lymphoma (under clinical trial for ALCL)	NSCLC	Already developed#
Colchicine, Anti-inflammatory agent	Gout (Gouty arthritis)	Pericarditis	Already developed*
		COVID-19	Under development*
Daunorubicin, Antibiotic		Breast cancer	Already developed*
Digoxin, Cardiotonic	CVDs such as heart failure	Prostate Cancer	Under development*
Dimethyl fumarate, Anti-allergic	Psoriasis	Multiple sclerosis (MS)	Already developed*
Disulfiram, Acetaldehyde dehydrogenase inhibitor	Chronic alcoholism	Cancer	Under development*

Drug, pharmacological category	Original indication	New indication	Status of development
Duloxetine, SSNRI	Depression	Generalized anxiety disorder, fibromyalgia, chronic musculoskeletal pain, neuropathic pain	Already developed*
Everolimus, Immune suppressant	Immune suppressant	Pancreatic neuroendocrine tumors	Already developed*
Favipiravir, Anti-viral	Influenza	COVID-19	Under development*
Fluorouracil, Antimetabolite, Anti-cancer	Cancer	Breast cancer	Already developed*
Fluoxetine, Anti-depressant	Depression	Premenstrual dysphoria	Already developed*
Gabapentin, Anti-epileptic	Epilepsy	Neuropathic pain	Already developed*
Galantamine, AChE inhibitor	Neuromuscular paralysis	AD	Already developed*
Hydroxychloroquine, Anti-malarial	Malaria, RA	COVID-19	Under development*
Ibudilast, PDE inhibitor (Anti-asthmatic)	Asthma	Neuropathic pain	Already developed*
Imatinib, TKI (Anti-cancer)	CML, ALL	GIST	Already developed*
Isoniazid, Anti-tubercular	Tuberculosis	Certain types of tumor	Already developed*
Itraconazole, Anti-fungal	Fungal infections	Cancer like NSCLC (Anti-angiogenic)	Under development*
Ivermectin, Anthelmintic (Anti-parasitic)	Scabies, river blindness, helminthiasis	COVID-19	Under development*
Lopinavir/Ritonavir, Anti-viral	HIV/AIDS	COVID-19	Under development*
Metformin, Anti-diabetic	DM (type 2)	Breast and colon Cancer, CVDs	Under development*
Methotrexate, Anti-metabolite (Anti-cancer)	Cancer	Psoriasis, RA	Already developed*
Milnacipram, Anti-depressant	Depression	Fibromyalgia	Already developed*
Miltefosine, Anti-leishmanial	Cancer	Leishmaniasis, Amoeba infection	Already developed*
Mifepristone, Antiprogestin	Termination of pregnancy in combination with misoprostol	Cushing's syndrome	Already developed*
Minoxidil, Vasodilator (Anti-hypertensive)	Hypertension	Androgenic alopecia	Already developed*
Nelfinavir, Anti-viral	HIV/AIDS	Breast cancer, NSCLC (under clinical trials)	Under development*
Nitroxoline, Anti-bacterial	UTI	Breast, bladder and pancreatic cancers	Under development*

Drug, pharmacological category	Original indication	New indication	Status of development
Orlistat, Anti-obesity agent	Obesity	Cancer	Already developed*
Penfluridol/Pimozide, Anti-psychotics	Psychiatric illness	Breast cancer	Under development*
Propranolol, β-Blocker	Hypertension	Migraine	Already developed*
Remdesivir, Anti-viral	Influenza, Ebola (failed in clinical trial)	COVID-19	Under development#
Retinoic acid	Acne	Acute leukemia	Already developed*
Ribavirin, Anti-viral	Viral infection such as RSV, hepatitis C infections	Cancers like leukemias and lymphomas	Under development*
Ritoximab			
Ropinirole, Anti-Parkinsonian drug	PD	Restless leg syndrome	Already developed*
Sildenafil, PDE inhibitor	Angina pectoris, Pulmonary arterial hypertension	Erectile dysfunction	Already developed*
Simvastatin, Hypolipidemic	CVDs	Lung cancer	Already developed*
Sunitinib, TKI (Anti-cancer)	Imatinib-resistant GIST, RCC	Pancreatic neuroendocrine tumors	Already developed*
Tamoxifen, Anti-estrogen (Anti-cancer)	Breast cancer, Anticancer	Systemic lupus erythematosus	Already developed*
		NTDs like Leishmaniasis (in combination with miltefosine)	Under development*
Thalidomide, Immune modulator	Immunomodulation, Morning sickness (withdrawn)	Multiple myeloma, Leprosy	Already developed#
Tocilizumab, IL-6 inhibitor (Immune modulator)	RA	COVID-19	Under development*
Topiramate	Fungal infections	IBD	Already developed*
Valproic acid, Anti-epileptic	Epilepsy	Manic depression (bipolar disorder), migraine headache	Already developed*
Valsartan, ARB (Anti-hypertensive)	Hypertension, Heart attack	AD	Already developed*
Zidovudine, Anti-viral	Cancer (failed clinical trial)	HIV/AIDS	Already developed#

**Indicates successful repositioning from FDA approved drug.*
#Indicates successful repositioning from investigational new drug (IND).
AD: Alzheimer's disease; AChE: acetylcholine esterase inhibitor; ALCL: anaplastic large cell lymphoma; ALL: acute lymphocytic leukemia; ALK: anaplastic lymphoma kinase; ARB: angiotensin-receptor blocker; CML: chronic myeloid leukemia; COVID-19: coronavirus diseases-19; COX: cyclooxygenase; CVDs: cardiovascular diseases; DM: diabetes mellitus; GIST: gastrointestinal stromal tumor; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; IBD: inflammatory bowel disease; IL: interleukin; NSAID: non-steroidal anti-inflammatory drug; NSCLC: non-small cell lung carcinoma; NTD: neglected tropical diseases; PD: Parkinson's diseases; PDE: phosphodiesterase; RA: rheumatoid arthritis; RCC: renal cell carcinoma; RSV: respiratory syncytial virus; SSNRI: selective serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TKI: tyrosine kinase inhibitor; UTI: urinary tract infections.

Table 3.
Examples of some repositioned drugs from approved and investigational drugs [24–29].

7. Opportunities and challenges

On contrary to traditional drug discovery program (a complex and time consuming process with high cost of development and risk of failure), drug repositioning, reduces the time and cost of drug development. Drug repositioning is also a low-risk strategy. Computational or machine learning approach has significantly improved the performance of drug repositioning. In comparison to computational approaches, using experimental approaches (such as target protein-based screening, cell-based assay, testing in animal model, and clinical testing) that provide direct evidence-based understanding of links between drugs and diseases are more reliable and credible. However, in recent years computational approaches are usually combined with the experimental approaches to identify new indications for old drugs, called mixed approaches. In this approach, computational methods are validated by biological experiments and clinical tests. Mixed approach of repositioning offers a rational and exhaustive exploration of all possible repositioning opportunities, taking into consideration improved access to available databases and technological advances. Furthermore, the R&D investment required for drug repositioning is lower than that for traditional drug discovery. Thus, drug repositioning offers an opportunity for many pharmaceutical companies to develop drugs with lower investments [27, 28]. Mixed approach of DR offers opportunities for developing repositioned drugs more effectively and rapidly. From the market perspective, a large number of diseases require new drugs to be treated with a potential market demand and economic impacts. For example, the discovery of drugs for rare/neglected diseases has a large potential market to explore. There is, therefore, an opportunity for repurposing of drugs for the treatment of rare, neglected, orphan diseases or difficult to treat diseases. There are over 6000 rare diseases that lack proper treatment. About 5% of them are being researched. Rare diseases have a large potential market to explore. Given the high attrition rates, substantial costs and slow pace of drug discovery and development, repurposing of old drugs to treat both common and rare diseases is increasingly becoming an attractive area of research because it involves the use of drug molecules with reduced risk of failure at shorter time and lower cost development [30–33].

With the advent of technologies such as genomics, proteomics, transcriptomics, metabolomics, etc., and availability of huge databases resources including drug omics data, disease omics data, etc., there are a plenty of opportunities to discover drugs by drug repositioning in a collective and integrated effort of all the above methods/approaches mentioned above. Researchers are currently equipped with the latest reliable tools and data to explore the novel unknown mechanism of actions/pathways based upon disease-specific target proteins/genes and/or specific biomarkers associated with the progression of the disease [34, 35].

Various databases and software are available publicly for genomics, proteomics, metabolomics and pathway analysis. Several computational strategies are already developed to increase the speed and ease of the repurposing process. Some important databases used in drug repositioning studies are outlined in **Table 4**.

However, opportunities come often with many challenges in drug repositioning. The identification of a new therapeutic indication for an existing drug poses a major challenge in repositioning. However, drug repositioning is a complex process involving multiple factors such as technology, commercial models, patents, and investment and market demands. Some multiple challenges which include choosing the right therapeutic area for the drug under investigation, issues related to clinical trials such as need to run new trials from start if the data from clinical or preclinical trials for the original drug or drug product are outdated or are not satisfactory [34, 35].

Information available about	Database	Website
Chemical structure	PubChem	http://pubchem.ncbi.nlm.nih.gov
	Drugbank	http://www.drugbank.ca/
	Chemspider	http://www.chemspider.com
	ChemDB	http://www.chemdb.com
	Therapeutic Target Database (TTD)	http://bidd.nus.edu.sg/group/cjttd/
Target 3D structure	RCSB Protein Data Bank (PDB)	http://www.rcsb.org
	OCA	http://oca.weizmann.ac.il/oca-bin/ocamain
	Proteopedia	http://proteopedia.org
Drug-target information	Drugbank	http://www.drugbank.ca/
	Therapeutic Target Database (TTD)	http://bidd.nus.edu.sg/group/cjttd/
	Pharmacogenetics Knowledge Base (PharmGKB)	http://www.pharmgkb.org/
	DrugMap Central (DMC)	http://r2d2drug.org/index.html
Protein interaction information	Human Protein Reference Database (HPRD)	http://www.hprd.org/
	Biological General Repository for Interaction	http://thebiogrid.org/
	Database of Interacting Proteins (DIP)	http://dip.doe-mbi.ucla.edu/dip/Main.cgi
	STRING	http://string-db.org/
Pathway information	NCI Pathway Interaction Database (NCI-PID)	http://pid.nci.nih.gov/
	Kyoto Encyclopedia of Genes and Genomes (KEGG)	http://www.genome.jp/kegg/
	PathwayCommons	http://www.pathwaycommons.org/about/
Clinical trial information and adverse effects	Clinicaltrial.gov	http://clinicaltrials.gov
	Adverse Reaction Database (Canada)	http://www.fda.gov/Drugs/
	SIDER	http://sideeffects.embl.de/
FDA label information	FDALABEL (US FDA)	http://www.fda.gov/ScienceResearch/
	DailyMed (US FDA)	http://dailymed.nlm.nih.gov/dailymed/about.cfm
	Structured Product Labeling (SPL)	http://www.fda.gov/ForIndustry/DataStandards/
Omics data (Target/Drug)	NCBI-GEO	http://www.ncbi.nlm.nih.gov/geo/
	Sequence Read Archive (SRA)	http://www.ncbi.nlm.nih.gov/Traces/sra/
	ArrayExpress	http://www.ebi.ac.uk/arrayexpress/
	Cancer Cell Line Encyclopedia (CCLE)	http://www.broadinstitute.org/ccle/home
	Sequence Read Archive (SRA)	http://www.ncbi.nlm.nih.gov/Traces/sra/

Table 4.
Databases used in repositioning studies [34–36].

8. Regulatory and intellectual property issues

Traditional drug development strategies are costly, failure prone and expensive ventures. Therefore, drug repositioning has recently drawn considerable attention to discover drugs with new therapeutic uses with the goal to bring drugs out at comparatively faster rate for clinical use. Some regulatory issues that are commonly encountered in drug repositioning are described as follows [37, 38]. As per regulatory guidelines, new preclinical and/or clinical trials may be required to be carried out if the available data are not satisfactory and do not comply with the requirements of regulatory agencies such as FDA or EMA. Another important issue is related to patent application and intellectual property rights (IPR). There are no provisions of IP protection of drug discovery by repositioning approach as per the IP and patent laws. For repositioned drugs, IP protection is limited. For repositioning drugs, IP protection is limited. For example, some novel drug-target disease associations found by repositioning researchers were confirmed by publications or online databases; however, it is difficult to seek IP protection for such associations because of the law. The IP issue prevents some repositioned drugs from entering even into the market [39, 40]. Moreover, some repositioning projects are forced to be abandoned, which is a waste of time, money and lot of efforts. Although many omics data and medical databases have been established, selecting the appropriate approach for repositioning is still a challenge due to the regulatory issues because massive amounts of data may not be valid if not obtained from reliable sources. It is, therefore, necessary that researchers or manufacturers must strictly adhere with standard regulatory guidelines for drug discovery by repositioning approaches [2, 41–43].

9. Conclusion

Traditionally, the dug repurposing has a long recorded history discovery of drug molecules particularly through serendipitous observations. In recent years, it has embarked a new avenue in the development of new therapies based upon existing/approved medicines. The strategic drug repositioning in a more systematic and rational way has brought innovation with the discovery of drug molecules with unknown therapeutic indications. As drug repositioning approach offers significant reduction in R&D costs, greater chances of success, shorter research time and lower investment risk, it has gained increasing market demands. Because these advantages are beneficial for discovery scientists, drug researchers, consumers and pharmaceutical companies, enabling the application of novel approaches of repositioning strategy in the drug discovery program for almost all human diseases. Moreover, the use of *in silico* techniques along with the application of structure-based drug design (SBDD) and pharmacophore modeling strategies and artificial intelligence (AI) technology can further accelerate the process of drug purposing in the drug discovery program. In the era of precision medicine, the drug repositioning strategy has become very much useful to establish the unknown mechanism of action of drugs through exploration of novel disease/metabolic/signaling pathways, or off-targets and target-specific mechanisms/ genetic expression profile for even genetic disorders. Advancement in genomics have provided us with genomic and transcriptomic data in huge quantities using technologies like next generation sequencing, microarray data and transcriptomics, etc. Network biology and systems biology approaches may add additional benefits to unveil such novel mechanisms of actions with through insights into drug-target interaction profile at molecular/genetic level. For better drug repositioning, more in-depth understanding are required to be executed

with integrated approaches between computational and experimental methods to ensure high success rates of repositioned drugs. However, drug repurposing can be successfully utilized in the discovery and development of new drugs with novel and effective therapeutic indications for human diseases.

Conflict of interest

Authors declare that there is no conflict of interest.

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