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DRUG REPURPOSING: A SHORTCUT TO NEW BIOLOGICAL ENTITIES

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Drug repurposing has proved to be an efficient alternative to drug discovery owing to the facts that it is economical and risk factors being much lower or even negligible as the drug has already been approved for having safe use in humans. The contrast of drug discovery from drug repurposing, its advantages and the challenges faced during the process are the important factors to be considered in drug repurposing. The approaches in drug discovery include three methods namely computational, biological and mixed. Moreover, the recent advancement in application of drugs for COVID-19 proved drug repurposing is a vital strategy in medical science for the upcoming years.

Keywords: drug discovery; drug repurposing; strategies; approaches; computational; biological; COVID-19; advantages; methodologies; repurposed drugs.

1. INTRODUCTION

Drug repurposing, also known by the names of drug repositioning, drug retasking, drug re- profiling, drug recycling, drug redirection and therapeutic switching, can be defined as a process of recognition of new pharmacological indications from old/existing/failed/investigational already marketed/FDA approved drugs/prodrugs and the application of newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use [1].

It is well known that the cost of development of a new drug is extremely high and runs in 800 million–1.5 billion US dollars. Besides this, it takes anywhere between eight to ten years, to discover a new drug. After starting with 100,000 New Chemical Entities (NCEs), one ends up with two to four molecules, which can be called as new drugs to put on the market. The failure rate is very high in clinical trial of new drug; out of which nearly 50% drug fails in phase 3 out of the total cost of 800 million US dollar, nearly 400 million dollar goes in clinical trial and other process of new drug development [2].

Drug repurposing, also generally regarded as drug repositioning or drug rescue, emerged fundamentally in the early 1990s as a feasible alternative to the conventional drug discovery process. Repositioning depends on two prime scientific bases:

(1) The discovery, through the human genome elucidation, that few diseases share sometimes common biological targets, and

(2) The concept of pleiotropic drugs [3].

Repurposers have an advantage because they are working with compounds that have been approved or at least put through millions of dollars worth of preclinical and early clinical testing. As a result, repurposing can get drugs to the market cheaper and faster than the lengthy new drug research and development. Moreover, whereas 10% of new molecular entities are able to make it to the market from Phase II clinical trials and 50% new entities from Phase III. The rates for repurposed compounds are 25 and 65% for Phases II and III, respectively [4].

2. TRADITIONAL DRUG DISCOVERY VERSUS DRUG REPURPOSING

2.1. Traditional Drug Discovery Steps:

(i) **Discovery and preclinical study** (average 6.5 years). Research for a new drug starts in the laboratory and animal testing to answer basic questions about safety.

(ii) **Safety review** (average 30 days). Review to ensure animal testing and assure safety.

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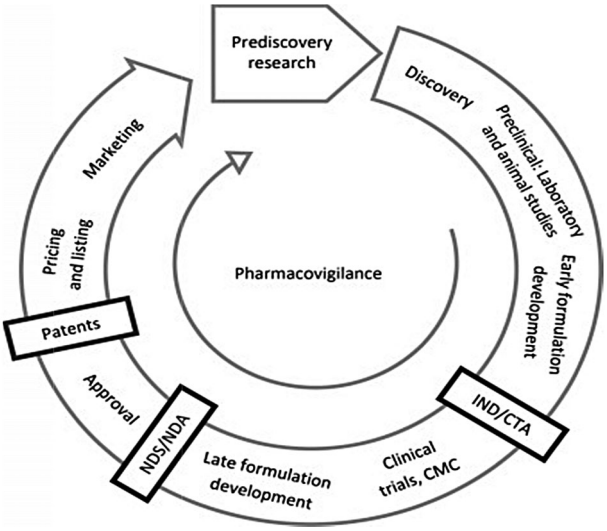


Fig. 1. The Life Cycle of pharmaceutical products [6].

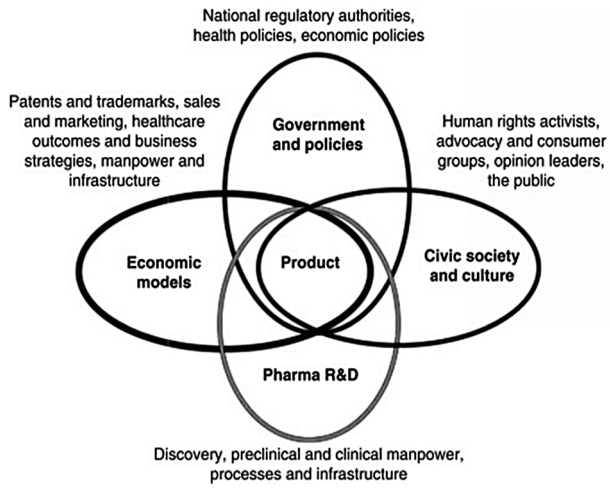


Fig. 2. Cross-functional interaction in pharmaceutical ecosystem [7].

(iii) **Clinical research phase 1** (average 1.5 years). This step includes the first trial in humans and is primarily concerned with the safety, pharmacokinetic and pharmacodynamic profiles of the drug. The drug is initially given as single, very low dose, then in gradually increasing amounts and subsequently, in multiple doses. Phase 1 trials only involve a small number of subjects and are generally conducted in normal volunteers.

(iv) **Clinical research phase 2** (average 2 years). Studies commonly referred to as phase 2 are relatively small-scale studies involving patients with the target disease or condition.

(v) **Clinical research phase 3** (average 3.5 years). If the drug in question proves safe in second phase, then phase three is carried out. This means that large numbers of patients are studied in medical centers throughout the country.

(vi) C**linical research phase 4** (average 1.5 years). In this step, the drug is already approved by FDA. It is frequently termed as post marketing surveillance. These tests are generally large-scale and designed primarily to investigate the incidence of rare adverse reactions and to check if drug recall is required [5].

The typical pathway for a traditional drug discovery and development process or the Life Cycle of a pharmaceutical product is depicted in Fig. 1.

The pharmaceutical ecosystem can be stated as the convergence of networks of cross-interacting subsystems across the drug product pipeline, which has a stake in the efficiency of drug development and access to marketed drug. The tools for streamlining the utility of drug during pre- and post-marketing stages include the strategic issues, regulatory organizations and reforms, local and national cultures, politics, federal laws, economic and reimbursement policies, intellectual property and patent policies, product related factors. There are networks of multichannel interactions at various levels around the development of pharmaceutical product [7]. The scheme of cross-functional interactions in pharmaceutical ecosystem is shown in Fig. 2.

2.2. Drug Repurposing Steps:

(i) C**ompound identification** (1.2 years). Compound identification is to select candidate drug for a particular drug target in the human organism.

(ii) **Compound acquisition** (0 – 2years). Getting licenses for the new candidate drug.

(iii) **Development** (1 – 5years). This step may start at preclinical, phase 1 or phase 2 drug research. To make sure that drugs are safe and effective, analysis of existing data is necessary.

(iv) **FDA post market safety survey**. FDA monitors all drug and device safety once products are available for use by the public [8].

Figure 3 compares the timelines for steps involved in Traditional Drug Discovery process and Drug Repurposing process.

2.3. Advantages of Repurposing Drugs

From the prior deliberation, it is evident that the drug repurposing approach is beneficial from the fact that approved drugs and several discarded compounds have already been tested in humans and elaborative data is available on their pharmacology, dose, possible toxicity and formulation. Drug repurposing has numerous advantages over conventional drug discovery approaches, including:

(i) It considerably cuts research and development (R&D) expenditure.

(ii) It decreases the drug development timeline, as several existing compounds have already demonstrated as safe in humans, and hence does not require Phase 1 clinical trials.

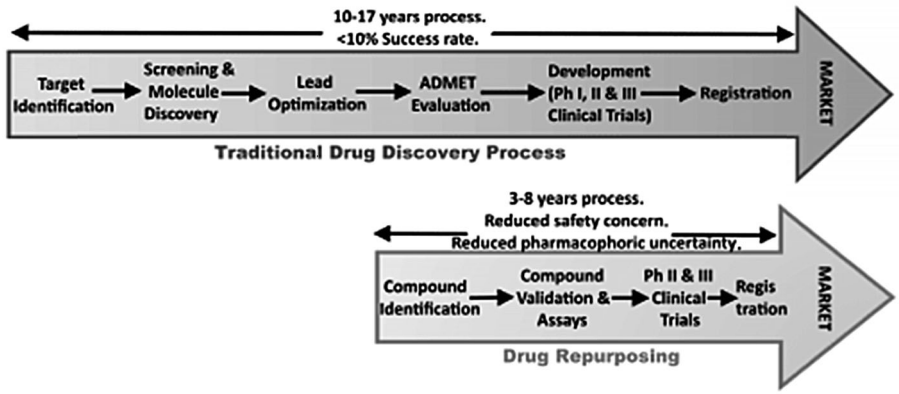


Fig. 3. Comparative timelines of traditional drug discovery and drug repurposing [9].

(iii) Potential for reuse of drug molecules in spite of adverse effects and failed efficacy in some indications [10].

2.4. Barriers of Drug Repurposing

In spite of several advantages associated with drug repurposing, the process suffers from certain hurdles. These mainly include:

(i) **Lack of clear regulatory pathways**. Pharmaceutical companies focus mainly on the development of new medicines and there is a lack of regulatory pathways to facilitate drug repurposing.

(ii) **Lack of financial incentives and research findings**. Pharmaceutical industry, including the generic sector, has hardly any incentive to invest in the research necessary to gain regulatory approval for a drug that is no longer under patent. This is because there is no return on investment anticipated, given the lack of intellectual property protection and low prices of generic formulation [11].

However, the drug repurposing process is a low-risk, high-rewarding strategy for developing drugs (Fig. 4).

2.5. Challenges Associated with Drug Repositioning

The foremost challenge encountered by scientists lie in the relatively weak intellectual property protection allotted to such medicinal products, which can reduce their return on investment and discourage companies from developing them [12]. As the concerned drug has earlier been patented as a new chemical entity, succeeding medicines containing the same entity can only be protected by a new application patent, possibly supported by a novel formulation procedure. Patents on applications are essentially limited rather than those for a new chemical entity in terms of the therapeutic uses they offer. Repositioned drug, still has the same chemical entity are not strong in the front of a potential legal challenge on the basis that the new indication was predictable from data in the scientific literature [11]. Another challenge is to convince the physicians that an already existing drug can be used for a completely new pharmacological indication. The comparatively weaker protection provided by these patents may nevertheless be offset by certain advantages granted to companies repositioning drugs for the treatment of orphan diseases (defined as diseases which are very rare) such as fee reductions and a guaranteed period of market exclusivity.

2.6. Strategies of Drug Repurposing

There are two main strategies for drug repurposing:

(A) On-target drug repurposing;

(B) Off-target drug repurposing**.**

These strategies for drug repositioning are schematically depicted in Fig. 5.

On-target drug repurposing. In the on-target strategy, we are investigating new indication of drug acting through the originally known target. The known pharmacological mechanism of a drug entity is applicable to a new therapeutic indication. In this strategy, the biological target of the drug

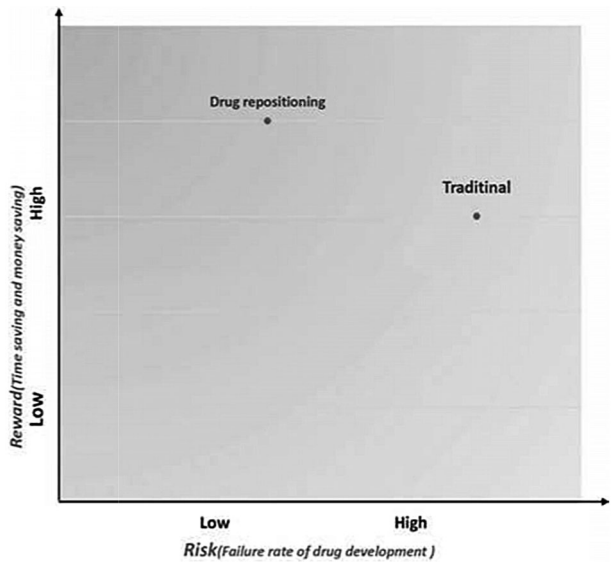


Fig. 4. Risk and reward of different drug development strategies [8].

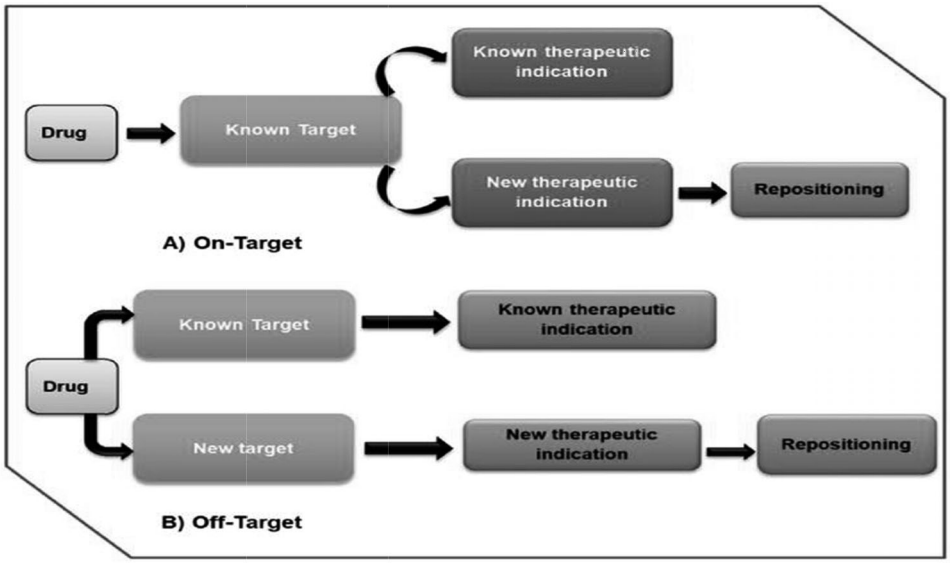


Fig. 5. On-target and off-target strategies for drug repositioning [12].

molecule remains same, but the disease is different. Appealing aspect is that it is likely to be compatible with dosing of the original drug. For example, an on-target strategy is observed in the repositioning of Minoxidil (Rogaine) as the drug acts on the same target and produces two different therapeutic effects. Minoxidil was repurposed from an antihypertensive vasodilator to an anti-hair loss drug. As an antihypertensive vasodilator, Minoxidil has the characteristic of widening blood vessels and opening potassium channels, which permits more oxygen, blood, and nutrients to the hair follicles and thus show its pharmacological action.

Off-target drug repurposing. In the off-target strategy, we discover new uses of a drug acting through an unanticipated target. The mechanism of action is not known. Drugs act on new targets, away from the original scope, for novel therapeutic indications. Therefore, the target on which the drug acts and the indication for which it is used, both are novel. Drug is primarily not optimized for the target, so one needs to be careful about the dosing. Methods such as docking and fingerprinting can be implemented. Aspirin (Colsprin) is an example of the off-target repurposing strategy, as it has been conventionally used as NSAID in the treatment of various pain and inflammatory disorders. Later it was discovered that it also suppresses blood coagulation (clot formation) by inhibiting the normal functioning of platelets, i.e., it acts as an antiplatelet drug. Hence, it is used in the treatment of heart attacks and strokes as well as in the treatment of prostate cancer has also been reported [12]. Refer Table 1 for indications, targets and novelty of the on- and off-target repurposing strategies.

TABLE 1. Indication, Target, and Novelty of On- and Off-Target Repurposing [12]

	Reformulation, Line Extension	On-Target Repurposing	Off-Target Repurposing	
Indication	Same	Different	Same	Different
Target	Same	Same	Different	Different
Novelty	Low	Same	High	Highest

2.7. Approaches of Drug Repositioning

Detection of novel drug–disease relationships being the main issue in drug repositioning, a number of approaches have been developed including:

- Computational approaches;
- Biological experimental approaches;
- Mixed approaches [12].

3. COMPUTATIONAL DRUG REPOSITIONING APPROACHES

Majority of the existing computational approaches are based on the gene expression response of cell lines after treatment or merging several types of information about disease–drug relationships. They are divided into three categories, including:

- Network based approaches;
- Text mining approaches;
- Semantic approaches.

3.1. Network Based Drug Repositioning

Network based computational approaches are broadly utilized in drug repositioning due to associated ability to integrate multiple data sources, which are further classified as follows.

Network based propagation approaches employ prior data propagate from the source hubs to all network hubs and some sub-network hubs. According to different propagation ways, these approaches can be partitioned into two types. The local propagation approaches only take the limited information into consideration and may fail to make accurate predictions. The global propagation approaches employ data from the entire network enabling them to perform better than local approaches, which is why most current researchers concentrate on global approaches to achieve outstanding results. For example, Kohle, et al. [*Am. J. Hum. Genet*., **82**(4), 949 – 958 (2008)] developed a network propagation based on the global information of a network to find novel disease gene interaction, which included three phases: (a) extracting drug disease relationship and constructing a disease gene network, (b) obtaining the global information of the network using random walk propagation algorithm in the network, and (c) defining global metrics to predict novel disease gene relationships, which performed better than other approaches.

Network based cluster approaches have been put forward to discover the relationships between novel drug disease or drug target on the basis of the fact that biologic entities such as disease, drug, protein, etc. in the same module of biological networks share similar characteristics. These approaches intend to find several modules also known as clusters, groups or cliques using cluster algorithms in accordance with the topology structures of networks. The modules employ various (e.g., drug–drug or drug—target) relationships [13]. Characteristics of network based computational approaches are presented in Table 2.

3.2. Text Mining Based Drug Repositioning

The extraction of novel and biological entity relationships from the literature has been a challenge. Text mining techniques have been widely used to tackle this problem and have been developed to mine new information from scientific literature as well as identify relationship between biological concepts or biological entities. The fundamental pipeline of biological text mining comprises four stages:

(i) Information retrieval (IR), whereby relevant documents are extracted from the literature, further filtered to eliminate irrelevant concepts in document;

(ii) Biological name entity recognition (BNER), whereby valuable biological concepts are identified with controlled vocabularies;

(iii) Biological information extraction (BIE);

(iv) Biological knowledge discovery (BKD).

In the BIE and BKD steps, useful information is extracted to discover knowledge about biological concepts to build a knowledge graph, at the same time potential associations between knowledge such as drug- disease and drug- tar-

TABLE 2. Network Based Drug Repositioning [14]

Name	Method	Network	Description	Key Findings	Advantage	Disadvantage
RNSA	Cluster	PPI	A global network algorithm to identify protein clusters on PPI network	Some complex proteins	This method considers both local and global information from networks. Overlap clusters can be detected as well.	Some information may be dropped as the cluster size is small
RRW	Cluster	PPI	An effective network cluster approach to identify protein clusters on a PPI network	Some complex proteins	This is a general method with high prediction accuracy.	It is a time costly and memory costly method that cannot detect overlap clusters
ClusterONE	Cluster	PPI	A global network algorithm to identify node clusters on network	Some complex proteins	This approach outperformed the other approaches including MCI, RRW, etc. both on weighted and unweighted PPI networks	There is not a standard gold value to evaluate clusters
	Cluster	Drug protein disease	A variant clusterONE algorithm to cluster nodes on heterogenous networks	(iloperidone, schizophrenia) Hypertension	This is an efficient cluster approach that integrates multiple databases	It Is difficult to distinguish between positive associations and negative associations on the network
	Cluster	Drug target disease	An algorithm to detect clusters on the network	(Vismodegib, Basal cell carcinoma) gorlin syndrome	This is a genera and highly robust approach	This approach loses weakly associate genes o diseases and drugs
MBiRW	Cluster	Drug disease	A bi random walk based algorithm	Levodopa, Parkinson disorder > Alzeihmer	Predictions of this approach are reliable	This approach needs to adopt more biological alternatives

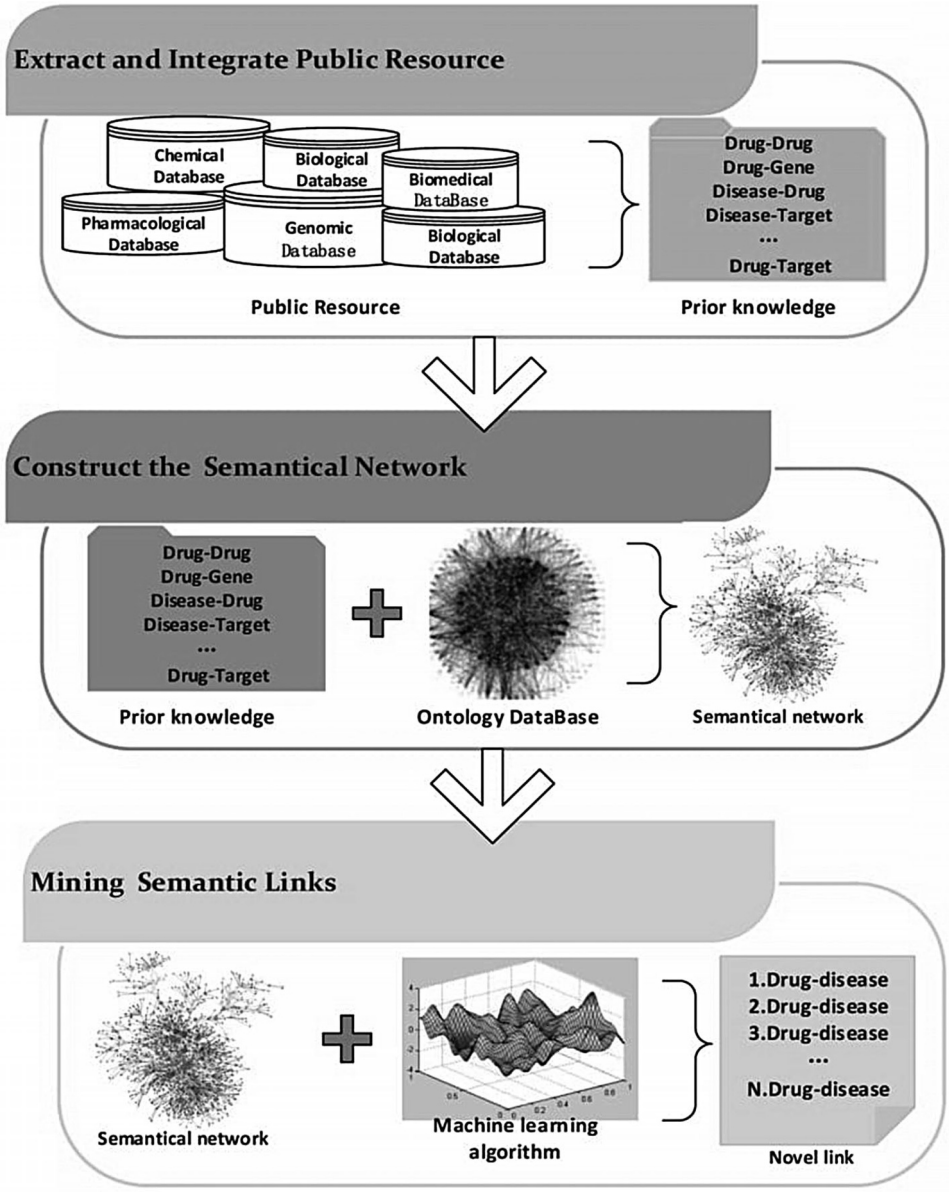


Fig. 6. The workflow of semantic network interference [8].

get relationships can also be detected [13]. Text mining based computational approaches are presented in Table 3.

3.3. Semantics Based Drug Repositioning

Semantics based approaches are widely used in information retrieval and image retrieval and recently have been applied to drug repositioning. The work flow in these methods mainly includes three steps.

(i) Biological entity relationships are extracted from prior data in huge medical databases to construct the semantic network;

(ii) Semantics network based on existing ontology networks are constructed by adding the prior information obtained in previous step;

(iii) Finally, mining algorithms are designed to predict novel relationships in the semantic network [15]. **T**he workflow of semantic network interference is illustrated in Fig. 6.

4. BIOLOGICAL EXPERIMENTAL DRUG REPOSITIONING APPROACHES

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

involve target screening approach, cell assay approach, animal model approach and clinical approach [12].

5. MIXED APPROACHES

In recent years, numerous scientists have combined computational approaches and experimental approaches to find new indications for drugs, called "Mixed Approaches", wherein the result of computational methods was validated by biological experiments and clinical tests. Mixed approaches provide opportunities to researchers for developing repositioned drug effectively and rapidly [12]. Refer Fig. 7 for an overview of drug repositioning approaches.

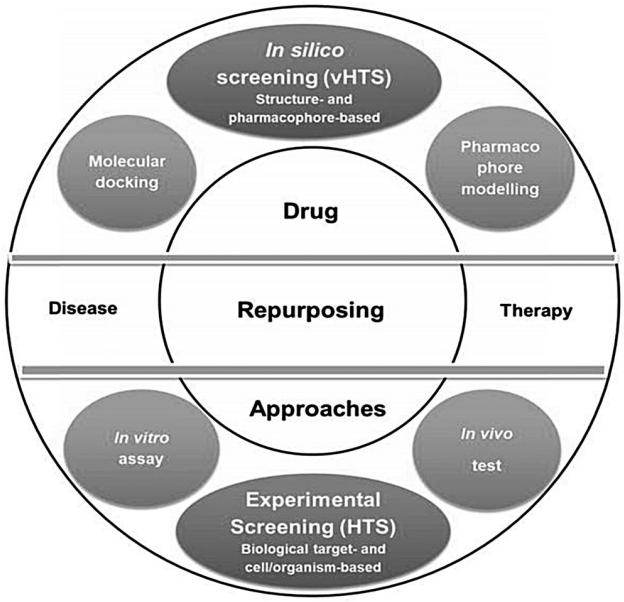


Fig. 7. Approaches of drug repurposing [12].

6. METHODOLOGIES OF DRUG REPURPOSING

The methodologies adopted in drug repurposing are extensively divided into three categories depending on the quantity and quality of the pharmacological, toxicological and biological activity-related information available:

(i) *Drug Oriented Methodology*: The structural characteristics of the dug molecules, biological activities, adverse effects and toxicities are evaluated, meant for identifying molecules with biological effects based on cell/ animal assays. This type is based on traditional pharmacology and drug discovery where studies are usually conducted to determine the biological efficacy of drug molecules without having an estimation about biological targets.

(ii) *Target Oriented Methodology*: It comprises *in silico* screening or virtual high throughput screening of drugs or compounds from drug libraries/ compound databases such as ligand based screening or molecular docking followed by *in vitro* and *in vivo* throughput and/or high content screening of drugs against a selective protein molecule or a biomarker of

TABLE 3. Text Mining Tools for Drug Repositioning [15]

Name	Class	Input	Output	Description
Biovista	Static	Biological knowledge	Gene protein relationships	A mining framework to extract gene protein relationships
Biowisdom	Static	Ontology	Drug disease, drug target relationships	A platform to discover novel biological entity relationships
FACTA+	Static	Tekst	Abstracts and linked concepts	A system to find associated concepts based on a user query
EDGAR	Static	UMLS term	Drug gene relationships	A system to extract relationships between drugs an genes involved in cancer using syntactic analysis.
Polysearch	Dynamic	Document	Knowledge	A web based text mining and natural language processing platform
Extract 2	Static	Bio entities	Entity relationships	A text mining based tool to map biological entities to ontology / taxonomy entries
Anni 2.0	Static	Bio entities	Linked concepts	An ontology interface of a text mining tool to extract
DrugQuest	Static	Drugs	Drug drug relations	A knowledge discovery tool to detect drug drug relationships
MaNER	Dynamic	Medical document	Revelant entities	A rule based system to mine relevant entities in medical documents
BEST	Dynamic	Biomedical literature	Relevant bioentities	A knowledge discovery system to extract relevant bioentities

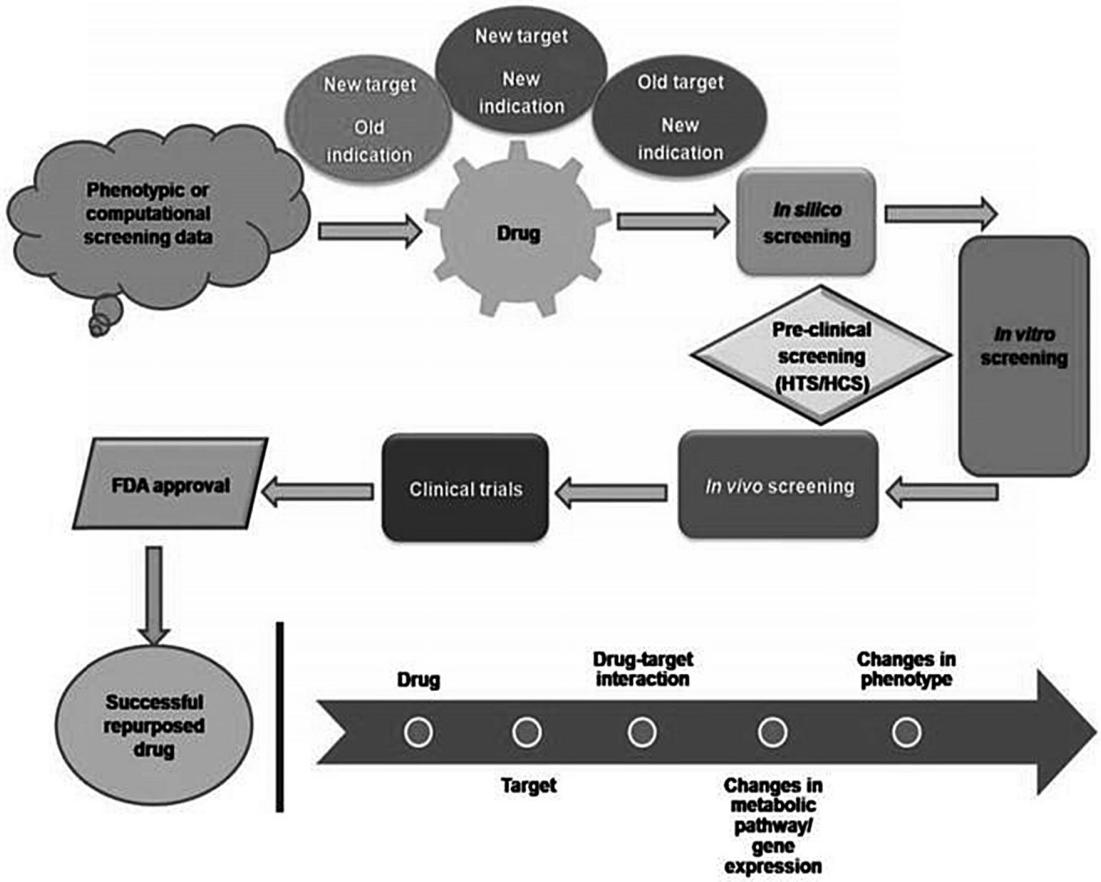


Fig. 8. Methodologies and steps in drug repositioning [12].

interest. There is a prominent success rate in drug discovery as compared to drug oriented method as most biological targets represent the disease pathways/mechanisms.

(iii) *Disease/Therapy Oriented Methodology*: It is relevant when there is more information on disease model available, as drug repurposing can be guided by the disease and/or treatment based upon availability of information concerning the disease process provided by

(i) Proteomics, data on disease specific target proteins;

(ii) Genomics, data on disease specific genetics;

(iii) Metabolomics, disease specific metabolic pathways/profiles;

(iv) Phenotypic data, on off-target mechanisms, pharmacological targets, disease pathways, pathological conditions, adverse and side effects [12].

Methodologies and steps of drug repositioning are summarized in Fig. 8.

7. DRUG REPURPOSING IN COVID-19

7.1. History

The first case of novel coronavirus was identified in the end of December 2019 in Wuhan, China, where 27 cases of atypical pneumonia were recorded [16]. Since then, coronavirus disease has spread worldwide and on 11th March 2020 it was declared as pandemic by World Health Organization [17].

7.2. COVID-19 / SARS-CoV

COVID-19 is acute respiratory syndrome which affects respiratory system and causes pneumonia leading to acute respiratory distress syndrome (ARDS), multi organ failure and death [18]. COVID-19 also known as coronavirus disease is an infectious disorder caused by coronaviruses (CoV). The name "coronavirus" refers to the crown-like projections on the surface of pathogens. Fever, dry cough, difficulty in breathing, chest pain and other respiratory illnesses are symptoms of COVID-19. The coronavirus spreads through respiratory droplets produced when an infected person coughs, sneezes or talks. Spread is growing when people are in close contact within 6 feet [19].

7.3. Mechanism of SARS-CoV Infection

For any viral infection to occur binding of viruses to a host cell through target receptor is necessary. The invasion of CoV into the human cells is a complex process [20]. To enter

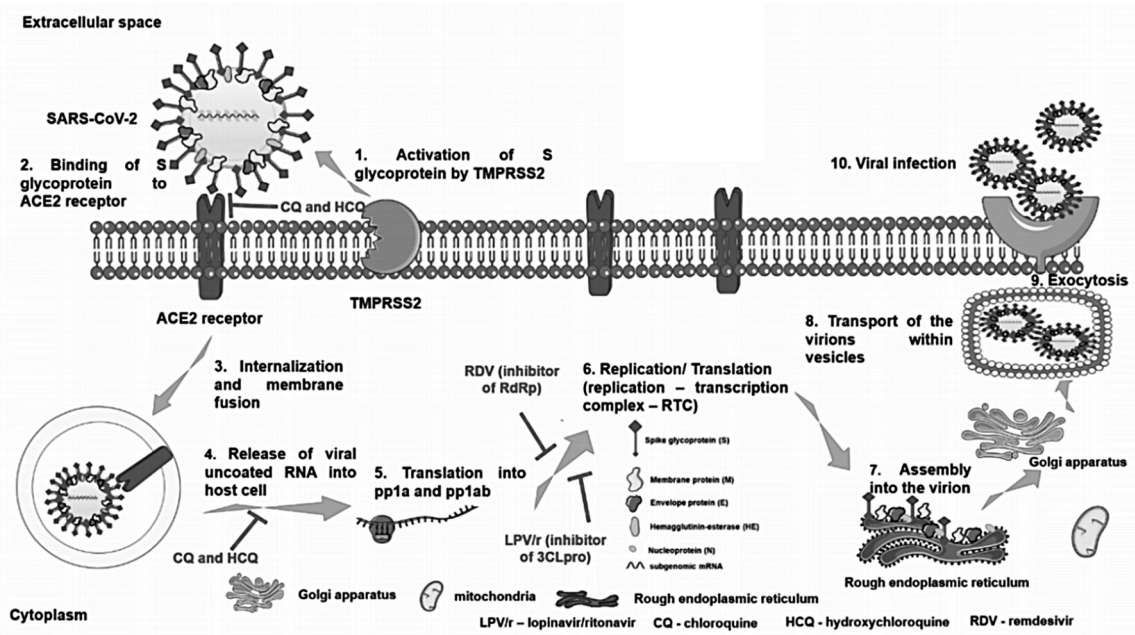


Fig. 9. Mechanisms of action of SARS-CoV [21].

into a cell, SARS-CoV and SARS-Cov-2 both requires interaction of spike glycoprotein with angiotensin converting enzyme-2 (ACE-2). The ACE-2 protein provides an easy entry for SARS-CoV [21].

The viral S glycoprotein consists of two subunits, S1 and S2, S1 is responsible for the virus attachment to the host cell surface though the receptor-binding domain (RBD), whereas S2 is needed for the fusion of the viral and cellular membranes. SARS-CoV and SARS-CoV2 mainly infect airways and alveolar epithelial cells, macrophages. The affinity of CoV is dependent on the ability of S protein to interact with the receptor of host cell [18]. Binding of S spike glycoprotein to the human ACE2 receptor by epithelial respiratory cells, vascular endothelial cells are essential for Human infection of COVID-19 [21]. Mechanisms of action of SARS CoV are illustrated in Fig. 9.

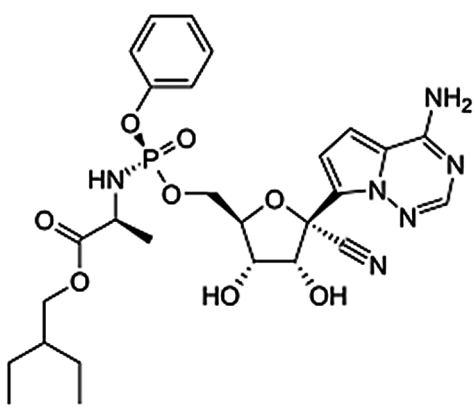
7.4. Drug Repurposing Approaches in COVID-19

There are three types of approaches computational approaches, biological experimental approaches, and mixed approaches. Computational methods are new and useful in the drug repositioning. This method gives brief information about interaction between SARS-CoV and human host cell, protein-protein interaction, drug target in human, this information helps in identification of repurposed drug [4]. According to WHO Report, the antiretroviral drugs like Favipiravir and Remdesivir, antimalarial drugs Chloroquine and Hydroxychloroquine, and HIV drugs like Lopinavir and Ritonavir are mostly repurposed in the treatment of COVID-19/SARS-CoV [22].

7.5. Drug Repurposing Strategies for COVID-19

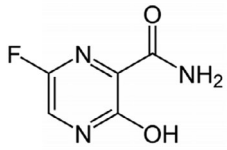
The drug-repurposing work process is organized distinctively from conventional drug development. In drug repurposing, there are lesser steps and different parameters to follow, namely compound identification, compound acquisition, development and FDA post-marketing surveillance. Computational drug-repositioning approaches implemented on COVID-19 can be widely categorized as (i) network-based models, (ii) structure-based approaches, or (iii) machine/deep learning approaches. There are some literature works that used hybrid approaches, and it is classified, for example, a method consisting of both network and clustering as network based if network modeling is considered to be prevalent over machine learning [23].

7.6. Examples of Repurposed Antiviral Drugs in SARS-CoV19



Remdesivir

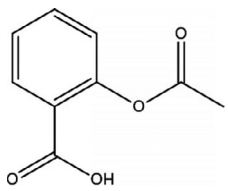
Remdesivir, an antiviral agent, is the monophosphoramidate prodrug nucleoside analog. The drug was developed to treat infections caused by Ebola viruses but was found to be effective against multiple RNA viruses including parainfluenza type 3 virus, measles viruses, nipah virus. Remdesivir is considered as the most promising repurposed drug against COVID-19 infection as it efficiently inhibits SARS-CoV2 infection in human. In Italy, Remdesivir is prescribed to the patients 200 mg per 12 hours as a loading dose followed by 100 mg per 12 h via intramuscular route for 10 days in the treatment of COVID-19 with other palliative medications while in Washington USA, Remdesivir was given intravenously for 7 days to the patients who were hospitalized for the treatment of COVID19. The FDA approved Remdesivir in emergency use for the treatment of COVID-19 patients in critical conditions. Japan has also approved the use of Remdesivir in the management of COVID-19 [18, 22].



Favipiravir

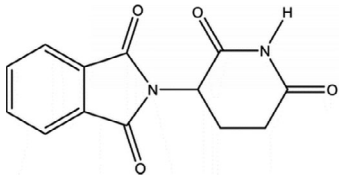
Favipiravir is a potential antiviral agent developed by Toyama Chemical Co. Ltd., Japan. Favipiravir is a nucleic acid purine base analog, 6-fluoro-3-hydroxy-2-pyrazinecarboxamide approved for treatment of influenza in Japan. Mechanism of action of this drug is inhibition of RNA dependent RNA polymerase. Favipiravir undergoes metabolism in the liver mainly by aldehyde oxidase. Favipiravir-ribofuranosyl-5'-triphosphate is an active metabolite of Favipiravir that is responsible for its pharmacological effect. As per clinical data, recovery rate of COVID-19 patient is increased in co-morbidity free patients. Favipiravir has been approved for treatment of COVID-19 in China on 15th February, 2020 as well as in Russia for the treatment of hospitalized COVID-19 patients [20, 22].

8. EXAMPLES OF REPURPOSED DRUGS FOR VARIOUS DISEASES



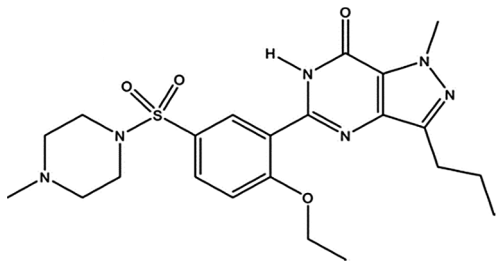
Aspirin

It is an oldest example of drug repurposing. Aspirin is an acetylsalicylic acid having analgesic used non-steroidal anti-inflammatory drug (NSAID) and anti-inflammatory effect. It inhibits the activity of the enzyme called cyclooxygenase (COX) which is responsible to the formation of prostaglandins (PGs) that in turn lead to inflammation, swelling, pain and fever. Initially marketed by Bayer company in 1899 as an analgesic, Aspirin at low doses is repurposed as an anti-platelet aggregation drug. It may also be repositioned in the area of oncology in the treatment of prostate cancer [24, 25].



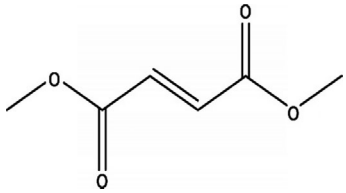
Thalidomide

Thalidomide was introduced as a safe antiemetic and hypnotic. It became popular for treating nausea and vomiting in early pregnancy. Unfortunately, drug caused teratogenicity and major birth defects. WHO banned Thalidomide in the year 1962. In 1964, Dr. Jacob Sheskin from Hadassah University, demonstrated its efficacy against erythema nodosum leprosum. However, in 1998 Celgene repositioned this drug as an orphan drug for complications of leprosy, but it strictly contraindicated during pregnancy. In 2006, Thalidomide was repurposed as a first-line treatment for multiple myeloma [24, 25].



Sildenafil

Sildenafil is a potential antihypertensive drug that causes vasodilation. It inhibits phosphodiesterase enzyme eventually leading to the inhibition of platelet aggregation. Because of these properties, it was earlier used as a promising treatment for angina, but later on, unexpected side effects like penile erections were observed during its clinical trial. Owing to this side effect, Pfizer company marketed sildenafil as a drug for erectile dysfunction in the year 1998. In 2005, Pfizer repurposed Sildenafil in the treatment of pulmonary arterial hypertension [24, 25].

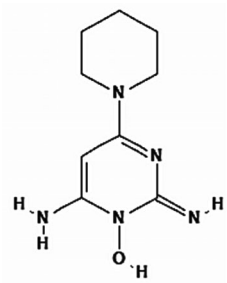


Dimethyl Fumarate

TABLE 4. Examples of Repurposed Drugs [27]

Drug Name	Class/ Action	Initial Use	Repurposed Use	Approval Status
Amantadine	Nmda Receptor Antagonist	Influenza	Parkinson's Disease	Approved
Aspirin	Nsaids / Salicylates	Analgesic	Antiplatelet Aggregation	Approved
Amphotericin-B	Antifungal Antibiotic	Antifungal	Visceral Leishmaniasis	Approved
Doxycycline	Tetracycline Antibiotic	Antibacterial	Malaria	Approved for prevention of Malaria
Galantamine	Cholinesterase Inhibitor	Polio, Paralysis	Alzeihmer's Disease	Approved
Minoxidil	Antihypertensive	Hypertension	Hair Loss	Approved
Zidovudine	Nrti	Anticancer	Antiviral	Approved
Dimethyl Fumarate	Methyl Ester of Fumaric Acid	Treat Allergies	Multiple Sclerosis	Approved for treating symptoms of multiple sclerosis
Thalidomide	Immunomodulator	Antiemetic in pregnancy	First Line Treatment Multiple Myeloma	Banned in pregnancy due to teratogenicity but approved in treatment of multiple myeloma
Sildenafil	Antihypertensive	Angina	Erectile Dysfunction/ Pulmonary Arterial Hypertension	Approved
Nelfinavir	Hiv Protease Inhibitor	Aids	Clinical Trial For Multiple Cancer	Not yet approved, under clinical trials
Sunitinib	Tyrosine Kinase Inhibitor	Renal Cell Carcinoma	Pancreatic Neuroendocrine Tumours	Approved

Dimethyl fumarate was first synthesized in 1819 as a mould inhibitor to protect leather. It was banned in Europe in 1988 due to the allergic skin reactions. It is commonly used in Germany to treat psoriasis, due to its anti-inflammatory activity under the brand name Fumaderm. Anti-inflammatory activity was regulated by increased expression of NRF2-dependent antioxidative genes. At higher doses, Dimethyl Fumarate was repurposed in the treatment of multiple sclerosis, under the brand name Tecfidera. It is less cardiotoxic and hepatotoxic than the other drugs used in multiple sclerosis. Dimethyl Fumarate was repositioned in multiple sclerosis based on similarity between the molecular profiles of psoriasis and multiple sclerosis [24, 25].



Minoxidil

Minoxidil is an antihypertensive agent. It is direct acting peripheral vasodilator which decreases blood pressure by decreasing peripheral vascular resistance. The metabolite of minoxidil, minoxidil sulfate, is responsible for its antihypertensive effect. Minoxidil is repurposed in the treatment of alopecia (hair loss). Topical application of Minoxidil promotes hair growth. It is also recommended to patients with alopecia areata and alopecia totalis [26].

TABLE 5. Repurposed Drugs Approved for Both Common and Orphan Diseases [4]

Compound	Common Disease	Orphan Disease	Approval Status
Azathioprine	Rheumatoid arthritis	Renal transplant	Approved
Bleomycin	Various cancers	Pleural effusion	Approved
Colchicine	Gout	Mediterranean fever	Approved
Cycloserine	Urinary tract infection	Tuberculosis	Approved
Eflornithine	Unwanted facial hair	Sleeping sickness	Approved
Cyclosporine	Rheumatoid arthritis Psoriasis	Transplant rejection	Approved
Everolimus	Renal cancer	Renal transplant	Approved
Histrelin	Prostate cancer	Precocious puberty	Approved
Interferon alpha	Hepatitis B and C	Various cancers	Approved
Rituximab	Rheumatoid arthritis	Various cancers	Approved
Infliximab	Ulcerative colitis Rheumatoid arthritis Psoriasis	Crohn's disease	Approved

For more examples of repurposed drugs refer Table 4. Repurposed drugs approved for both common and orphan diseases are presented in Table 5.

9. CONCLUSION

The traditional tedious drug discovery process has an embarked new way in the development of new therapies based upon existing/ approved medicine, better known as drug repositioning, a more strategic and rational approach. It has offered significant reduction in R&D cost, higher probabilities of success, shorter research time and much less investments. In pandemic like COVID-19 which hit the world badly, and urgent medicine was required in a short time, drug repurposing strategy worked quite well. Better understanding of the existing drug molecules, their structure, activity and structure activity relationship is required so as to ensure higher success rates in drug repositioning. However, this strategy can be effectively utilized in the discovery and development of new drugs with novel and efficient therapeutic indications for human use.

AUTHORS' CONTRIBUTIONS

Dr. (Mrs.) Nutan Rao designed the study and managed the work done. Ms. Ruksar Sande, Ms. Charvi Poojary, Mr. Tushar Poojari and Ms. Sonal Sawant drafted the manuscript with collective efforts.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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