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A Systematic Review on Drug Repurposing

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Abstract

Drug repurposing is a process of identifying novel potential or new clinical use or therapeutic use for approved drug or existing drugs that are outside the scope of the original medical indication. Drug repurposing is also called Drug repositioning, drug redirecting and drug reprofiling. This has become a popular strategy in recent years. This strategy is highly efficient, time saving, low cost and minimum risk of failure. This strategy maximizes the therapeutic value of a drug and consequently increases the success rate. The development of New Chemical Entity (NCE) or New Molecular Entity (NME) is a very time-consuming process, complex, lengthy, and risky process. So, it is better to develop new drugs by applying drug repurposing strategy in drug discovery and development program. This drug repurposing involves three types of approaches: computational approaches, biological experimental approaches and mixed approaches which are used to develop or identify the new use of drug molecules on a rational basis. This drug repurposing is a powerful tool for the researchers for the development of new drug or identifying new therapeutic use for old/ existing drugs and banned drugs. During Covid-19, various investigators were carried out to design novel drug molecules by using different approaches of drug repurposing to identify drug substances for treatment of Covid-19,which can acts as significant inhibitor against viral proteins. The methodologies involved in drug repurposing can be categorized into three groups such as Drug oriented, Target oriented and Disease or therapy oriented. The challenges and opportunities in drug repurposing can be discussed from multiple perspectives, including technology, commercial models, patients and investments.

Keywords:
Repurposing, drug discovery, clinical use, approaches, strategy, methodologies, and Covid-19.

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INTRODUCTION:

Drug repurposing or Drug repositioning is a process of finding new application or new pharmacological indication from marketed/ FDA approved drugs / prodrugs for the treatment of diseases other than the drug original therapeutic use. Traditional drug discovery is a time consuming, laborious, highly expensive and high-risk process [1]. According to a report by Eastern Research Group(ERG) it usually takes 10-15 years to develop a new drug. However the success rate of developing new chemical entity is only 2.01% on average . The number of drugs approved by FDA has been declined since 1995[3]. So that the drug repurposing process is implemented. There are four steps in drug repurposing for the development of new drugs: Compound identification, Compound acquisition, Development and FDA post marketed safety monitoring [2].

Traditional Drug Discovery vs Drug Repurposing:

There are two major steps of traditional drug discovery and development process [1].

1. Preclinical drug development
2. Clinical drug development
    1. **Preclinical Trial:** In this preclinical stage the therapeutic activity of the Active Pharmaceutical Ingredient (API) is determined in animals. After the preclinical trial on animal the drug goes to IND

(Investigational New Drug applications) and then goes to clinical trials.

2. **Clinical Trial:** The clinical trial stage involves 4 phases.

Phase-I (Human Pharmacology phase): In phase-I clinical trial, the activity of new drug molecule is determined in human volunteers. This phase involves up to 100 healthy human volunteers. The time required for this phase-I is about 1 month. This phase involves determination of adverse effects and risk benefit ratio [3].

Phase-II (Therapeutic exploratory Phase): In phase-II clinical trial, the safety and efficacy of a drug molecule for the treatment of a specific disease is evaluated. It involves the determination of Pharmacokinetic data. The time period required for phase-II is several months. This phase involves up to 100-1000 human volunteers [5].

Phase-III (Therapeutic confirmatory phase): In phase-III trial, the toxicological properties and safety of the drug is determined. In this phase the new therapeutic activity of the drug molecule is compared with existing Standard treatment. The time period required for this phase is several years. This phase involves more than 1000 human volunteers. After phase-III trial, the drug goes to NDA (New Drug Applications) and then goes to phase -IV clinical trials [4].

Phase-IV (Pharmacovigilance) : in this phase-IV trial, the new drug is approved and released into the market. The main objective of this phase is long term evaluation of some parameters such as mechanism of action and drawbacks of drug molecules. It is an ongoing phase.

This traditional drug discovery process in more lengthy and risky process. Drug repurposing is a simple and rapid process. It plays an important role in rapid drug discovery [5].

Figure-1: Traditional drug discovery versus Drug Repurposing process.

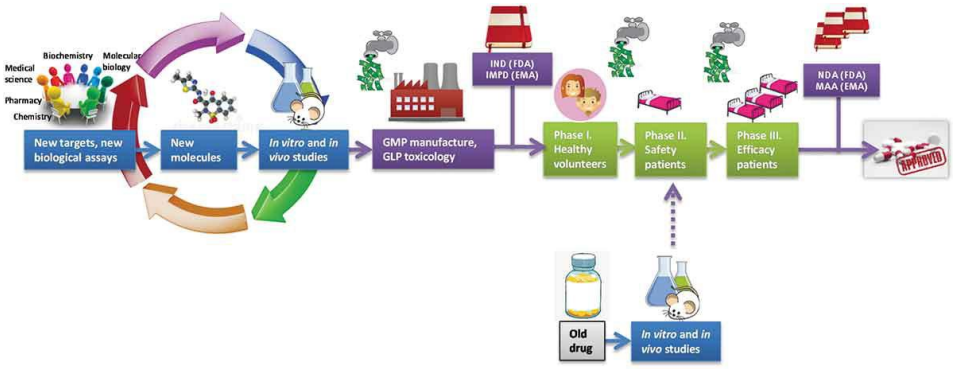


Table -1 : Difference between traditional drug discovery and Repurposing :

Traditional drug Discovery	Repurposing
1.More time consuming process.	1.Less time consuming process.
2.Highly expensive.	2.Low expensive.
3.High risk process.	3.Low risk process.
4.Low efficient.	4.High efficient.

Classification:

According to its target, drug repurposing is classified into two types such as on target repurposing and off target repurposing.

On target repurposing:

The biological target of the drug molecule is the same, but disease is different. In this type of repurposing the novel therapeutic effect is developed from the existing mechanism of action of a drug molecule [1]. For example, Sildenafil [6] is the first selective type 5 phosphodiesterase inhibitor, has evolved from a potential anti-angina drug to an oral treatment for erectile dysfunction and more recently to a new orally active treatment for pulmonary hypertension. Sildenafil is primarily used to treat angina pectoris, which is a intermittent chest pain or acute cardiac pain caused by inadequate blood flow and oxygen as a result of myocardial

ischemia [6]. It is also used in pulmonary hypertension [8], it is a condition in which the pulmonary arterial pressure increases above 25 or 30 mmHg at rest. In this condition Sildenafil acts by inhibiting the type 5 phosphodiesterase enzyme, thereby it decreases the degradation of cGMP (cyclic guanosine monophosphate) to cAMP (cyclic adenosine monophosphate). The increased levels of cGMP will reduce calcium ion levels and results in relaxation of blood vessels and lowers the blood pressure in the lungs [7]. This Sildenafil is repurposed to treat erectile dysfunction [6] (the inability to get and keep an erection firm enough for sex). During sexual stimulation this Sildenafil inhibits the PDE and there by increases the blood flow to penis and makes it erect for longer period of time.

Off target repurposing:

In this repurposing the biological target is different for different drugs. The novel therapeutic effect is developed through different mechanisms but not from the existing mechanism. For example, Amantadine [9] an anti-viral drug has evolved from an anti-influenza drug to an anti-Parkinson drug [11]. Influenza is a highly infectious, mild to severe respiratory disease of birds, humans and other animals that is caused by influenza viruses. Amantadine in influenza acts by inhibiting the uncoating of viral RNA in infected cells and thereby effectively prevents viral replication [10]. Parkinsonism is a neurodegenerative disorder that affects predominately the dopamine producing ("dopaminergic") neurons in a specific area of the brain called substantia nigra. This amantadine in parkinsonism acts by stimulating the dopamine receptors increasing the dopamine levels in the brain and improves the muscle control.

Figure-2: Mechanism of action of Sildenafil in angina, pulmonary hypertension, and erectile dysfunction (on target drug repurposing)

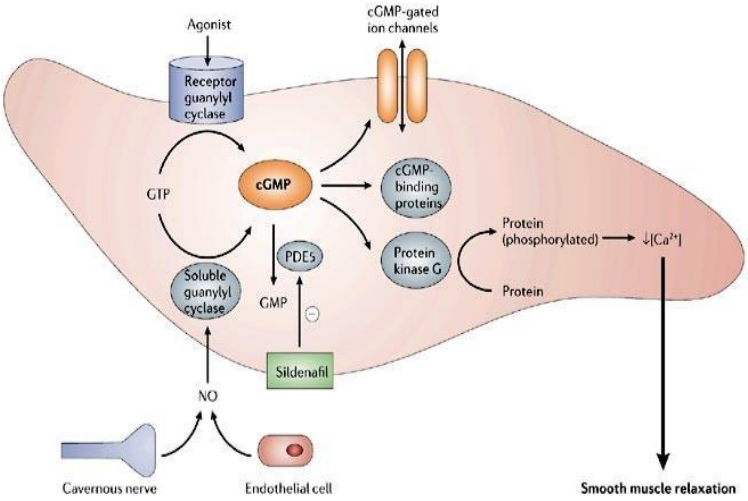
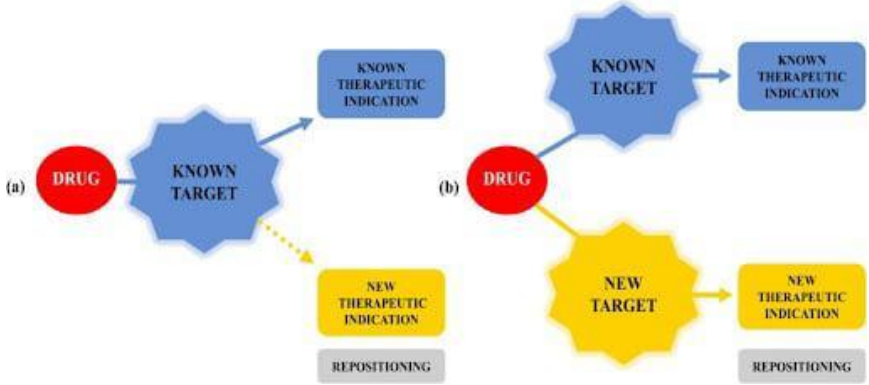


Figure-3 : a) on target drug repurposing b) off target drug repurposing.



Methodologies for drug repurposing:

Depending upon the quality and quantity of the pharmacological, toxicological, and biological activity information the methodologies for drug repurposing are categorized into three types: Drug Oriented, Target Oriented and Disease/Therapy Oriented [13].

Drug Oriented: This drug-oriented methodology is meant for identification of a drug molecule based on cell or animal assays. This methodology is based on traditional pharmacology and drug discovery principles. The biological efficacy of drug molecules is determined in the drug discovery principles without knowing about the biological target. The structural characterization, biological activities, adverse effects and toxicity are evaluated in this drug oriented methodology. In this if drug compound causes some desirable changes that time phenotype screening is used for identifying the drugs with biological action in cell or animal [12].

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: Methods used in drug repurposing.

Target Oriented:

This methodology comprises in silico screening or virtual high throughput screening(vHTS) drugs from drug libraries/compound databases such as ligand based screening or molecular docking followed by in vitro and in vivo high throughput screening (HTS) of drugs against a protein molecule [14].

Disease/Therapy Oriented:

In drug repurposing any diseases or treatments if there is more disease information available. In phenotypes diseases for information of how drugs modulate proteomics, genomics, metabolomics, or data concerning example: Proper information with possible off target mechanisms about adverse and side effects. In computational the network and pathway analysis methods are applied. It is a construction of metabolic pathways, networks of various diseases, targets key and recognize various protein molecules related to cell. These methods help to understand pharmacological targets [16].

Approaches for Drug Repurposing:

Drug repurposing has two approaches such as Computational Approach, Biological Experimental Approach.

Computational approach: computational approach or largely data driven; they involve systematic analysis of data of any type, which can lead to the formulation of repurposing. The most commonly used computational approaches are discussed below [14].

Signature Matching: It is based on the comparison of signature (unique characteristic) of a drug with other drug, disease, or clinical phenotype. The signature of drug could be derived from three general types of data: transcriptomic (RNA), proteomic or metabolomics data; chemical structure; adverse event profiles [15].

Transcriptomic signature matching can be used to make drug-disease comparisons and drug- drug comparisons.

Chemical structure signature matching is used based on chemical structure and their relationship to biological activity, comparing the chemical signature of one drug with other drug to see whether there are chemical similarities could suggest shared biological activity [18].

In adverse effect signature matching, every drug has a unique adverse effect profile that could be used as proxy for its phenotype. This adverse effect signature matching is based on hypothesis that two drugs that cause the same adverse effect may be acting on shared target or protein or on the same pathway [15]

Molecular docking: It is a structure based computational strategy to predict binding site complementarity between the ligand(drug) and target (receptor). If there is a prior knowledge of a receptor target involved in a disease, then multiple drugs could be interrogated against that particular target (conventional docking: one target and multiple ligands). Conversely, drug libraries could be explored against an array of target receptors (Inverse docking : several targets and one target) to identify novel interactions that can be taken forward for drug repurposing[15].

Genome-wide Association Studies:

The aim of this study is to identify genetic variants associated with common disease and there by provide insights into the biology of diseases and the data obtained may also help to identify novel targets, some of which could be shared between diseases treated by drugs and disease phenotypes studied by genome-wide association studies and there by leads to drug repurposing [18].

Pathway or Network Mapping : These approaches are widely used to identify drugs or drug targets that may have potential in repurposing. Network analysis involves conducting drug or disease networks based on gene expression patterns, disease pathology, protein interactions in order to aid identification of repurposing candidates. Pathway analysis of gene expression data sets from studies involving a wide range of respiratory viruses in human host infections models identified 67 common biological pathways that may be important In respiratory viral infections[14].

Retrospective Clinical Analysis: Use Of Electronic Health Records: Retrospective clinical data can be obtained from various sources, including Electronic Health Records (EHR), post marketing data and clinical trial data. EHRs contain an enormous amount of data on patients outcomes. The diagnostic and physiological data, including the results of laboratory tests as well as drug prescribing data, are more structured. However, EHRs also contains considerable amounts of unstructured Information's, such as clinical descriptions of patient symptoms and signs and imaging data. The wealth of data present in EHRs could be used as a source for identifying signals for drug repurposing. The best example of retrospective clinical analysis leading to repurposing of a candidate molecule is Sildenafil. The other examples include Aspirin in Colorectal cancer, Raloxifen in Breast cancer and Propranolol in Osteoporosis [15]

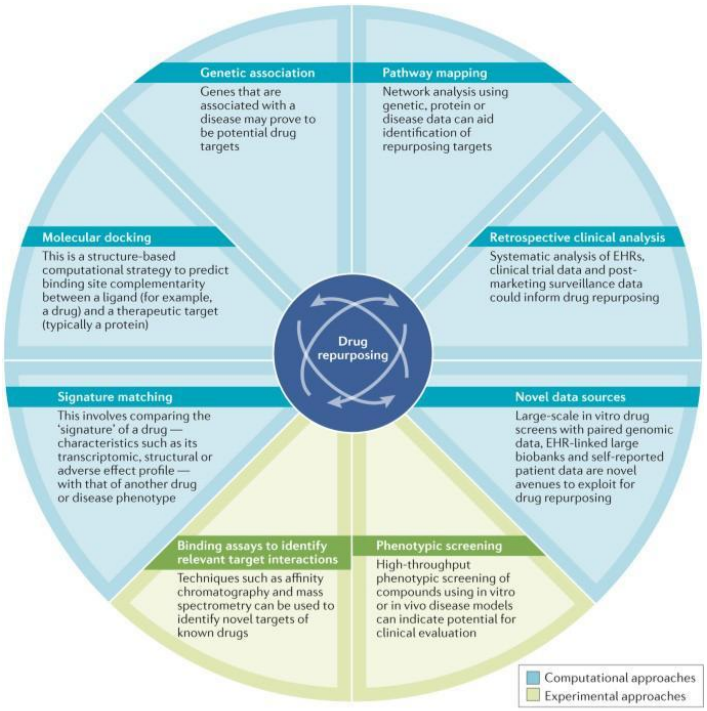
Novel sources of data for drug repurposing:

EHR linked large DNA Biobanks are considered as one resource for Drug repurposing. GlaxoSmithKline utilized China Kadoorie Biobanks, a prospective cohort of half a million individuals to examine the rate of PLA2G7 gene variants in major vascular

disease. Immortalized human cancer cell lines (CCLs) have been used in high throughput drug screens against hundreds of compounds to test their effect on cell viability. In several studies, the pharmacological data sets resulting from these screens have been nailed with comprehensive genomic characterization of the probed CCLs, thereby allowing identification of interaction between molecular features of cells and drug response. CCLs has been suggested as a novel resource for identifying drug repurposing opportunities[14].

Online self-reported patient data have been suggested as another new potential source for drug repurposing. One example is self-reported data on the usage of lithium carbonate by patients with ALS, which were used to derive useful conclusions about the efficacy of usage. Even though no effect of lithium on disease progression was identified, the approach suggests that data reported by patient over the internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drug already in use [15].

Figure-4; Approaches used in drug repurposing.



Experimental approach:

Binding assays to identify target Interactions: Proteomic techniques such as affinity chromatography and mass spectrometry have been used as approaches to identify binding partners for an increasing number of drugs. This technique includes the confirmation of cellular targets for the tyrosine kinase inhibitor (TKI) Crizotinib and the detection of Quinone reductase 2 as a cellular off target of acetaminophen. Chemical genetics can also provide a better understanding of the relationships between binding and efficacy in the cellular content. In turn these findings can be rapidly translated into new clinical areas or to address drug-resistance outcomes of prolonged exposure that are near – inevitable phenotypic responses to kinase inhibitor therapy in cancer[15].

Phenotype screening:

This screening can identify compounds that show relevant effects in model systems without prior knowledge of the target affected. in drug repurposing, if the compounds screened are approved or investigational drugs, this may indicate repurposing opportunities that can readily be pursued. Typically, in vitro phenotype screens use a wide range of cell-based assays in a 96-cell format [14].

Repurposed drugs:

Drug	Original indication	New indication
Amphotericin B	Fungal infection	Leishmaniasis
Aspirin	Anti inflammatory	Anti platelet
Amantadine	Influenza	Parkinson' Disease
Atomoxetine	Anti depressant	Attention deficit hyperactivity disorder
Astemizole	Anti histamine	Anti malarial
Avermectin	Elephantiasis	Tuberculosis
Bromocriptine	Parkinson's Disease	Diabetes Mellitus
Bupropion	Depression	Smoking cessation
Colchicine	Gout	Pericarditis
Celecoxib	Inflammation	Breast & colon cancer
Cimetidine	Gastric ulcer	Breast lung & prostate cancer
Denosumab	Osteoporosis	Crohn's disease
Duloxetine	Depression	Fibromyalgia
Dapoxetine	Depression	Premature ejaculation
Daunorubicin	Antibiotic	Breast cancer
Digoxin	Heart failure	Prostate cancer
Di methyl fumarate	Psoriasis	Multiple sclerosis
Disulfiram	Chronic alcoholism	Cancer
Eflornithine	Anti cancer	African sleeping sickness
Everolimus	Immune suppressant	Pancreatic neuroendocrine tumor
Fingolimod	Transplant rejection	MS
Fluorouracil	Cancer	Breast cancer
Fluoxetine	Depression	Premenstrual dysphoria
Gabapentin	Epilepsy	Neuropathic pain
Galantamine	Neuromuscular paralysis	Alzheimer's disease
Ibudilast	Asthma	Neuropathic pain
Isoniazid	Tuberculosis	Tumors
Itraconazole	Fungal infections	Cancers
Ketoconazole	Fungal infections	Cushing syndrome
Methotrexate	Cancer	Rheumatoid arthritis
Metformin	Diabetes Mellitus	Breast & colon cancer
Milnacipram	Depression	Fibromyalgia
Miltefosine	Cancer	Amoeba infections
Mifepristone	Oral contraceptive	Cushing syndrome
Minoxidil	Hypertension	Androgenic alopecia
Nelfinavir	HIV	Breast cancer
Nitroxoline	Urinary tract infections	Breast, bladder & Pancreatic cancer
Orlistat	Obesity	Cancer
Penfluridol	Psychiatric illness	Breast cancer
Propranolol	Hypertension	Migraine
Retinoic acid	Acne	Acute leukemia
Ribavirin	Hepatitis C	Leukemia
Rituximab	Various cancers	Rheumatoid arthritis
Raloxifen	Osteoporosis	Breast cancer
Ropinirole	Parkinson's disease	Restless leg syndrome
Sildenafil	Angina & pulmonary hypertension	Erectile dysfunction
Simvastatin	CVD'S	Lung cancer
Saracatinib	Anti cancer	Alzheimer's Disease
Topiramate	Epilepsy	Obesity
Tamoxifen	Breast cancer	Systemic lupus erythematosus

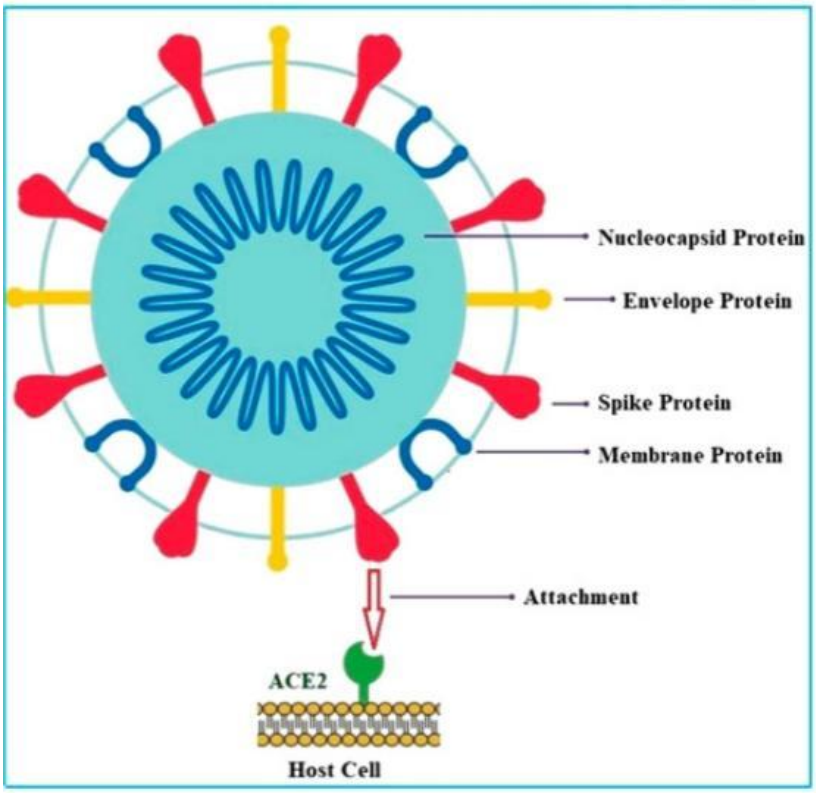
Table -3: repurposed drug

Drug repurposing in Covid-19:

Covid-19 is an infectious disease caused by a newly discovered virus known as Corona Virus. Covid-19 infections become major public health issue since December 2019. WHO declared Covid-19 as pandemic globally on February 11, 2020[19].

Corona virus disease was first discovered as an acute respiratory infection in the case of domestic chicken during 1980s. But the human corona virus was discovered in united states and united kingdom during 1960s[20].The corona virus cause severe and fatal respiratory tract infections in human beings. This corona virus is divided into four groups such as alpha (group-1), beta(group-2), gamma(group-3) and delta(group-4). Currently the entire world is under the threat of covid-19 (β corona virus/group-2). The structure of the corona virus is spherical or pleomorphic shape. It contains single stranded RNA genomes in size ranging from 26 to 32 kilo base with a nucleoprotein within capsid consisting of matrix protein [20]. Corona virus contains four types of proteins such as Spike(S), Envelop (E), Membrane (M) and Nucleocapsid protein. The Spike protein of corona virus plays a key role for induction of neutralizing antibody and T-cell response. The spike protein contains receptor binding domains (RBD) which binds with Angiotensin converting enzyme (ACE)-2 of host cell. This binding mediates fusion between cell membrane of host cell and virus particles [19].

Figure-5: Structure of corona virus and target binding sites.



Drug repurposing opportunities:

Rare and neglected conditions: Drug repurposing is a attractive approach for rare and neglected conditions, where the economics for developing a drug are unfavorable. A considerable fraction of the drug for neglected diseases. Initiative (DNDi)'s portfolio undergoing clinical trials corresponds to repurposed drugs [13].

In case of rare diseases, whose pathophysiology is often poorly characterized, computational techniques for predictive repurposing offer a quick way of identifying testable hypothesis that may translated into the clinical, with large-scale genome - sequencing initiative contributing to identify the genetic variations responsible for the disorder, and opening opportunities to rapidly repurpose drugs that target the correspondent proteins [21].

Precision medicine:

Precision medicine is an emerging approach that considers individual variability in genes environment, and lifestyle to each person to decide on or pursue an appropriate treatment. It is increasingly clear that some disorders with common traits that in the past were characterized as a single condition actually promise a spectrum of diseases and that more effective and for safe medications could be found if tailored to variations in an individual's genome,

transcriptions, proteome and metabolome , or to specific types of general condition[13].

Drug	Original indication	New indication
Azithromycin	Bacterial Infections	Covid-19
Chloroquine	Malaria	Covid-19
Colchicine	Gout	Covid-19
Favipiravir	Influenza	Covid-19
Hydroxychloroquine	Malaria	Covid-19
Ivermectin	Scabies	Covid-19
Lopinavir	HIV/AIDS	Covid-19
Ritonavir	HIV/AIDS	Covid-19
Remdesivir	Influenza	Covid-19
Tocilizumab	Rheumatoid arthritis	Covid-19

Table-4: repurposed drugs for covid-19

Systems medicine:

Systems medicine / network pharmacology offers an integrative perspective on previous paradigms in drug discovery: phenotypic-oriented and target oriented, 'rational' drug discovery. Network metabolic control analysis can be useful tools to design multi-target therapeutics or alternatively choose a synergistic drug combination drug repurposing can expand the horizon of drug repurposing, which has so far mostly explored repurposing known drugs as monotherapies. Synergistic drug combinations are an alternative approach to increase the success rate of drug repurposing [21].

Collaborative models:

These models can provide access to screening technologies that are difficult to acquire and maintain for most of academic institutions. New collaboration and business models are arising to bridge stake holders, including new funding models that welcome ventures capital and non-for-profit organizations. Such models might greatly impact certain fields of medicine where drug repurposing plays a prominent role. [21].

Drug repurposing challenges:

Intellectual property and economic considerations:

There are some legal aspects that could impair patenting a new medical use and the enforcement of patent rights, thus diminishing the incentives for drug repurposing. For drugs that are off patent, a patent for the new indication can be obtained but enforceability called become an issue if the new indication makes use of already available strength and dosage forms. Therefore, using the same strengths that were marketed for the original indication might be useful to exploit some of the advantages of drug repurposing [13].

Data and compound availability:

The open-source model is progressively gaining ground within the drug discovery community, public access to certain types of data is still limited. Even if accessibility was not an issue, some types of data are less friendly to data mining, integration and manipulation or are sometimes offered in a non-standardized manner. Integrating different types of data has also proven computationally demanding as it increases the power of analysis [21].

Compound availability with generic active pharmaceutical ingredients might occasionally also present some issues, especially if the compound is gone from the international market. Finding a reliable vendor in such circumstances might prove challenging [13].

CONCLUSION:

In this review conclude that the knowledge about drug repurposing. The repurposing of old / banned / existing drugs has many advantages in educational and research. It Is cost effective method. The repurposing studies must be defined by research centers, Universities, and pharmaceutical companies. The new indications are discovered for the old drugs. It is a powerful tool in drug discovery.

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