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Drug Repurposing: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author RTB designed the study and wrote the protocol for preparing the manuscript. Author SRB remove grammatical mistake, check spacing of the manuscript. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The drug development is a very time consuming and complex process. Drug development Process is Expensive. Success rate for the new drug development is very small. In recent years, decreases the new drugs development. The powerful tools are developed to support the research and development (R&D) process is essential. The Drug repurposing are helpful for research and development process. The drug re-purposing as an approach finds new therapeutic uses for current candidates or existing candidates or approved drugs, different from its original application. The main aimed of Drug repurposing is to reduce costs and research time investments in Research & Development. It is used for the diagnosis and treatment of various diseases. Repositioning is important over traditional approaches and need for effective therapies. Drug re-purposing identifies new application for already banned or existing drugs from market. In drug design, drug repurposing plays important role, because it helps to preclinical development. It reducing time efforts, expenses and failures in drug discovery process. It is also called as drug repositioning, drug redirecting, drug reprofiling.

Keywords: Repurposing; drug discovery; research and development; treatment; clinical trial.

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1. INTRODUCTION

In Drug Repurposing process finding new application of current candidate or drug existing from market due to side effect. It refers to the detection of new application from existing drugs/current candidate [1-6]. The uses of the newly identified drugs to the various diagnosis and treatment of diseases. Drug repurposing study used for the Old/Banned/Withdrawn formulation, dosage, Combination, Delivery, Failed drug, Approved drug, Current Candidate. Reuse of any drug granted by the Food Drug Administration. It is effective for treating another disease. In this discovery of new uses for failed drug candidates [7-12]. It is also termed as Drug re-positioning, re-purposing, re-profiling, re-directing or re-tasking.

The novel drugs development is a time consuming and complex process. In which investment rate is high and success rate being small [13-16]. In recent years, decreases the new drugs development or approved for the clinical use. Drug repurposing is powerful tools used to support the novel drug discovery process [17-21]. In genomics, bioinformatics and disease biology established clinical drug libraries availability and accelerated the both activity and in-silico based drug repurposing [22-24]. Drug repurposing is the process finding new uses of banned drugs from market [25-27].

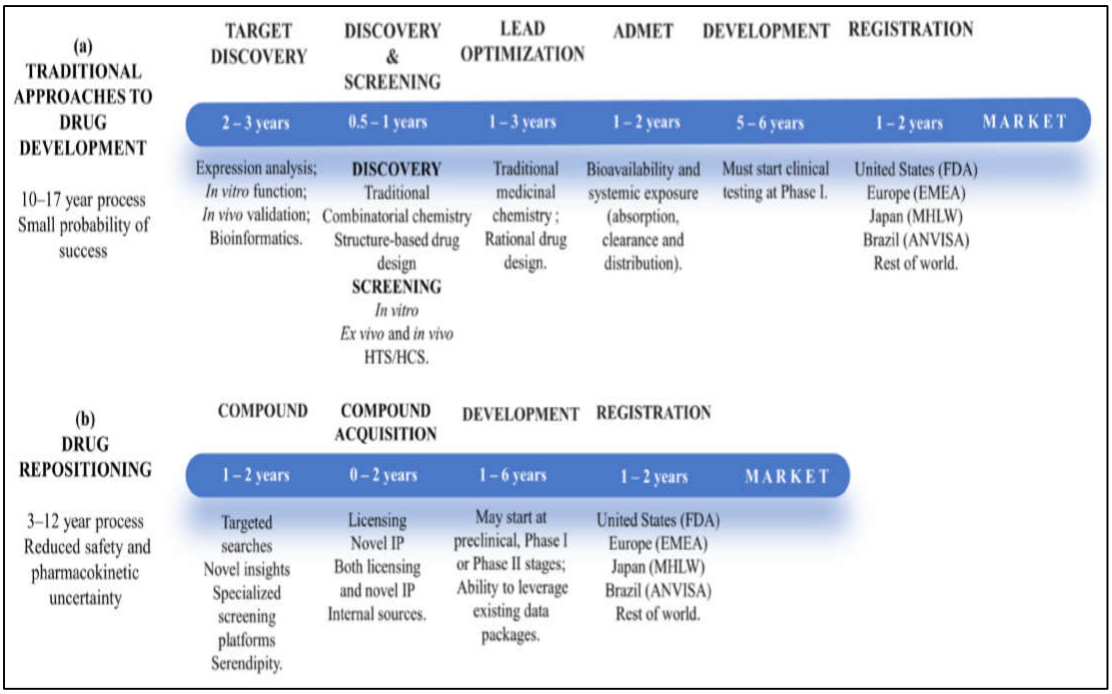

Fig. 1. Differentiate between traditional drug development and drug repurposing

Table 1. Important examples for drug repurposing

Drug Name	Category	Action	Repurpose
Aspirin	Analgesic & Antipyretic	Pain killer	Thrombosis
Sildenafil	Phosphodiesterase inhibitor	Erectile disfunction	Angina pectories
Thalidomide	Sedative	Morning Sickness	Erectile disfunction
Cyclosporine	Immunosuppressant	Suppress immune response	Antifungal
Itraconazole	Antifungal	Fungal infection	Anticancer
Nelfinavir	Antiviral	Viral infection	Anticancer
Nitroxoline	Antibiotic	Bacterial infection	Anticancer

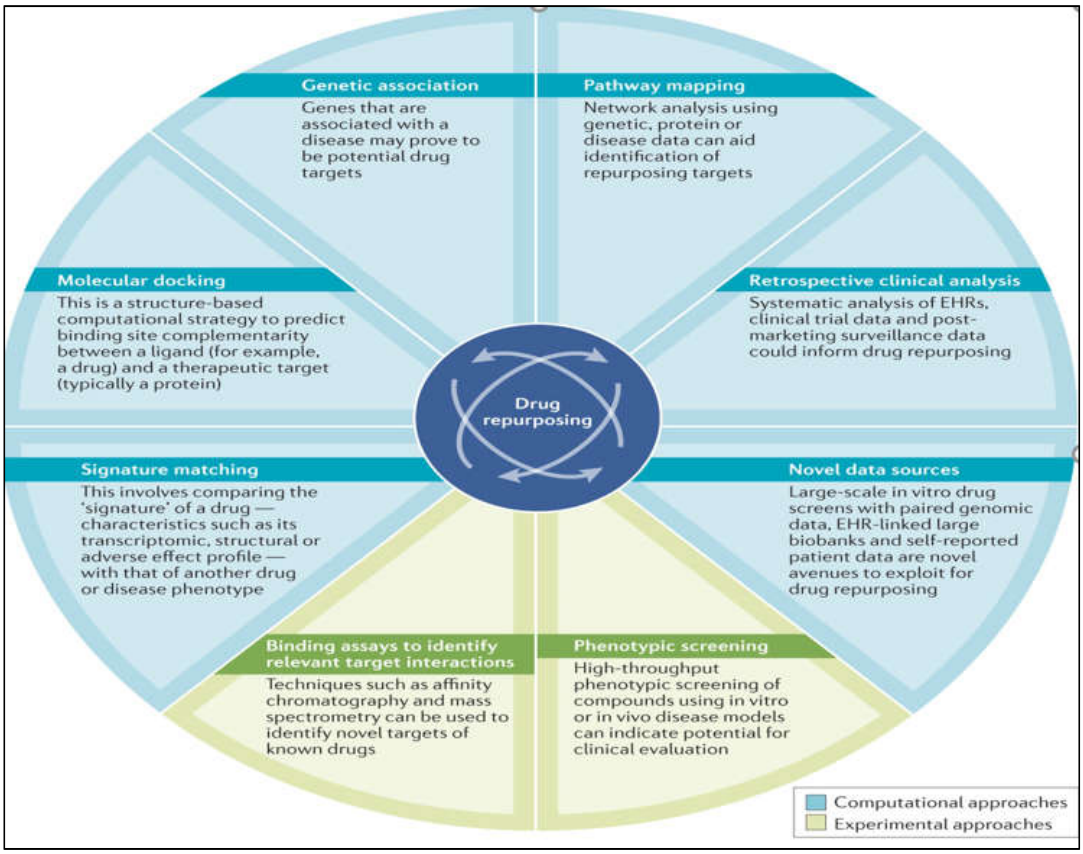

Fig. 2. Drug Repurposing

There are two major steps of traditional research and drug development process:

1. Preclinical drug development.
2. Clinical drug development.

The basically research is developed on the validation of a specific molecular target, new drug identification, new drug optimization, new drug determination [28-34]. The information about biological and toxicological Properties by using in-vitro and in- vivo model.

1. **Preclinical Trial:** It involves determination of pharmacological action of new chemical entity. It is Animal study. After the Preclinical trial on animal drug goes to Investigational New Drug (IND) and then goes to clinical trial.
2. **Clinical Trial:** It can be further subdivided into 4 phases.

Phase I: It is conducted in human volunteers. The sufferance of the new drug candidate is observed. In Phase I safe dosages measuring. It is Human Pharmacology phase. Up to 100 Healthy Volunteers used for phase I. It required one month time period. In this phase determine the Adverse effect and risk benefit ratio.

Phase II: In this evaluating efficacy and safety for the treatment of a specific disease. It is required for the drug development. It is Therapeutic Exploratory Phase. 100-1000 healthy as well as diseased Volunteers used for phase II. It required Several months for study. In this phase determine the pharmacokinetic data.

Phase III: It provide the toxicological properties and safety study of drug. In this the comparison between the existing standard treatment and new treatment of drug molecule. It is therapeutic Confirmatory phase. More than 1000 Diseased Volunteers used for phase III. It required Several years for study. It is used to comparison between drug under study and standard drug available in market.

After phase III drug goes to New Drug Application (NDA) and after NDA goes to Phase IV.

Phase IV: It is also termed as Pharmacovigilance. In this phase new drug is approved already in market. The long-term evaluation of some parameters is main objective of this phase such as mechanism of action and drawbacks of drug molecule. It is post marketing survey process [35-38]. It is ongoing phase. In this all type of diseased and healthy patient used.

The more investment and more efforts of some molecules achieve the promising results. In Phase II and III clinical stage the main developmental failure is occurs. It is mainly associated with safety and efficacy of drug. Drug repurposing is simple, rapid process play an important role for rapid drug discovery.

2. CLASSIFICATION

2.1 According to Its Targets

1) On target repurposing: If a mechanism of a drug is known that time finding new indications. If one molecule acts on the same target and they produce two dissimilar therapeutic action.

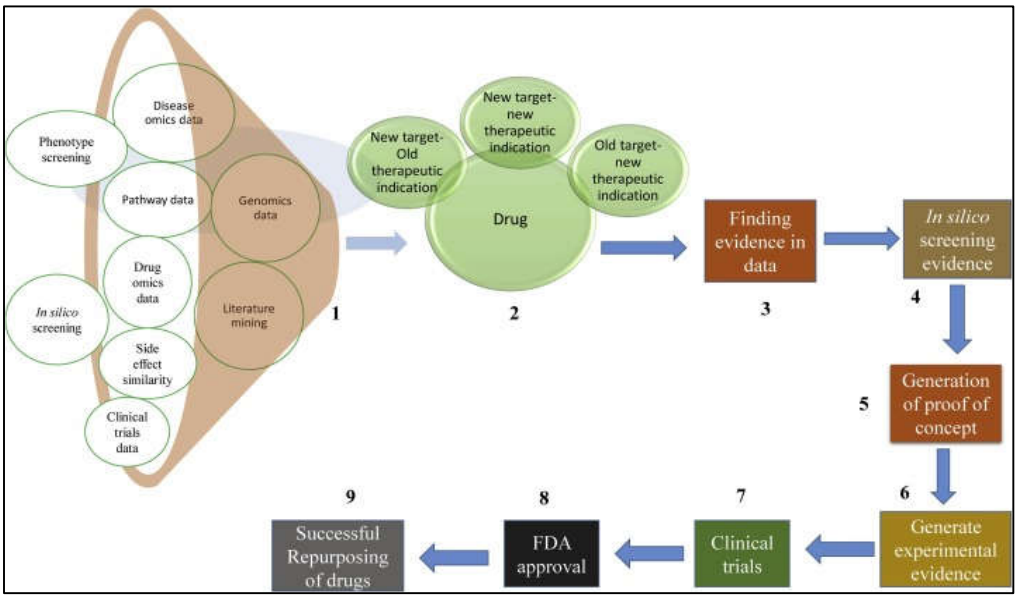

Fig. 3. Process drug repurposing

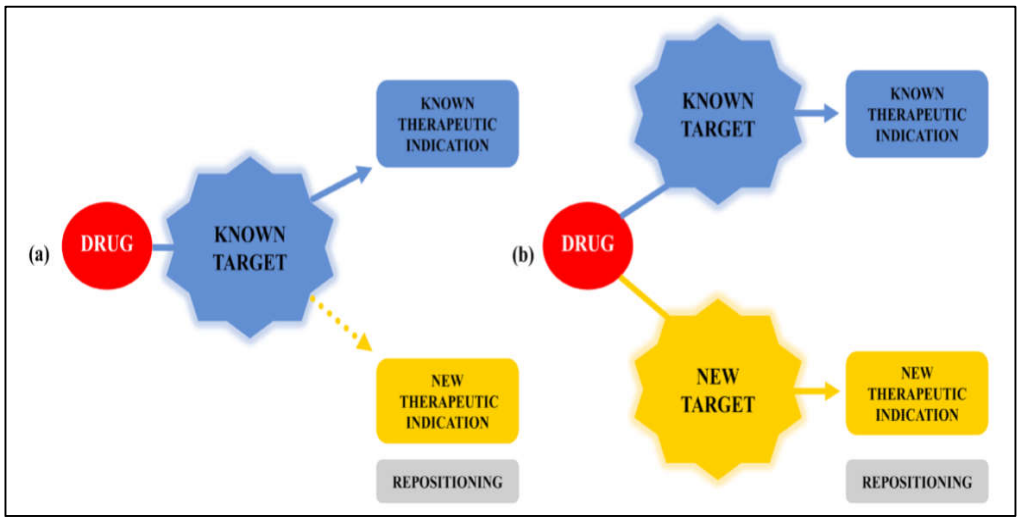

Fig. 4. a) On target repurposing, b) Off target repurposing

2) Off target repurposing: In this studying the chemical structure Finding new indications for a drug. In this repositioning the unknown Pharmacological mechanism. For finding the new therapeutic indications, Drug's act on another new targets, other than its actual use.

2.2 According to the Type of Approaches

1) Accidental and systemic approach.
2) Accidental approach: If new indication is accidentally discovered for banned or existing drug.
3) There are four type drugs can be repurposed by accident approach:
4) If the Molecule is used for a different disease.
5) It Dependent on the Target: In a disease is under investigation just imagine that a protein's role, but known drug for its own indication is accidently realized. It is affecting this protein molecule.
6) In development of a disease if another pathway is found to play a role that time researchers realize the drug molecule is able to increase that pathway or desirable action of drug.
7) A drug can be reused due to its side or adverse effects that time this drug adverse effect can be used for the treatment of another disease.

3. DRUG REPURPOSING TYPES

1. Drug Repurposing Based on Activity
2. Drug Repurposing Based on In-silico

3.1 Drug Repurposing Based on Activity

Advantage:

a) For target and cell- based no limitation for any screening assay
b) Validation of screening hits is Easy.
c) At that time of screening the false positive hits rate is lower.

Disadvantage:

a) It is Time and Labour consuming.
b) It Require the entire collection of previously existing drugs.
c) Screening assay development is necessary.

3.2 Drug Repurposing Based on In-silico

Advantage: It is time and Labour efficient process.

a) The entire collection of existing drugs is not necessary.
b) The screening assay development is not necessary.

Disadvantage:

a) For the screening assay of target and cell-based it produces drawbacks.
b) Require structure information
c) During screening false positive hits rate is high.

4. NEED OF DRUG REPURPOSING

1. Repurposing with Purpose
2. Repurposing with Strategy
3. Repurposing with Confidence

1. Repurposing with Purpose: The molecule used in drug repurposing is marketed drug discontinued in clinical trial due to reason other than protection concern.

a) Drug Centric repurposing
b) Disease centric repurposing

a) **Drug centric repurposing:** The discovering another indication for an existing drug. Pharmaceutical companies focused.
b) **Disease centric repurposing:** Identifying effective drug molecule for a disease.

2. Repurposing with Strategy: In this known safety profile of drugs and clinical trial for alternatives indication are cheaper. It is potentially faster process. It carries less risk than denovo drug discovery and development.

3. Repurposing with Confidence: The current success in drug repurposing has primary results of observed usefulness of repurposing.

Table 2. Subtypes of drug repurposing

Subtypes of drug repurposing	Examples
Prediction of Drug combination in repurposing	For block cancer survival pathways Target Inhibition networks were designed.
Electronic Health Record based drug repurposing	Electronic Health Record Data utilized for off-label drug uses drug repositioning trials and in clinical setting.
Fragment-based drug repurposing	Celecoxib is Nonsteroidal anti-inflammatory drug (NSAIDs) indicated as STAT3 inhibitors.
Genome-based drug repurposing	In drug repositioning it is used to prioritize targets for Data from genome-scale network.
Network-based drug repurposing	The networks of proteins like Knowledge of genes or co-expression networks and graph based or topological analyses. The small molecules evaluation done by this repurposing.
Neural network-based drug repurposing	The sensitivity prediction of chemogenomic drug by Neural network-based.
Off-targeting data driven repurposing	Nelfinavir is Antiretroviral drug. It is repositioned as anticancer molecule. It is based on molecule against Epidermal Growth Factor receptor by off-targeting mechanism.
Pathway based repurposing	It is based on gene expression analysis of human host in multiple respiratory viruses and Pathway based used for Drug targets were identified.
Driven prioritization of Protein-protein interaction repurposing	The pathophysiological mechanisms of syndrome elucidation are based on Protein-network.
Small Protein molecule interactions repurposing	In chemogenomic analyses De-novo target discovery and small Protein molecule interaction.
Drug repurposing based on Structure	Structure based used for the chemogenomic screening and polypharmacology indications are analyzing for drug scaffold refinement.
Systematic drug repurposing	For small cell lung cancer Tricyclic antidepressants were repositioned as inhibitors neuroendocrine tumors.
Text-mining driven drug repurposing	The drug repositioning for common properties of target proteins or drug molecule.
Topic modeling repurposing	Drug labels were analyzed by using Food Drug Administration to find drug pairs for common indications by Topic modeling.

5. METHODOLOGY

It is further classified into three types:

1. Drug-Oriented,
2. Target-Oriented,
3. Disease/Therapy-Oriented

1. Drug-Oriented: In drug-oriented mechanism the structural characteristics, adverse effect, side effect, phenotypic screening of drug molecule is evaluated. In this if the drug compound causes some desirable changes that time particular phenotype screening is used for identifying drugs with biological action in cell or animal [39-48]. It is based on traditional pharmacology. The new uses of drug discovered randomly, especially during the clinical Research and Development trials.

2. Target-Oriented: In target oriented the in vitro and in vivo high-throughput and high-content screening (HTS/ HCS) of molecule. It is used in In-silico screening of drugs and protein or a biomarker. It is ligand-based screening or molecular docking of drug molecule by drug libraries. The Comparison of drug-oriented methods overs the targeted-based methods.

3. 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. e.g., Proper information with possible off-target mechanisms about adverse and side effects [49-52]. In computational the network and pathway analysis methods are applied. It is construction of metabolic pathways, networks of various disease, targets key and recognize various protein molecule related to cell. These methods help to understand pharmacological targets.

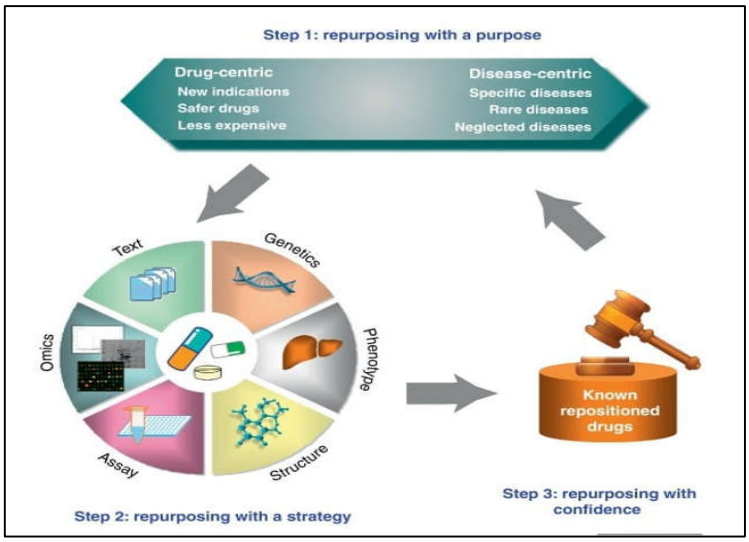

Fig. 5. Need of drug repurposing

6. CONCLUSION

In this review conclude that the knowledge about drug repurposing. The old/banned/existing drug repurposing that has been many advantages in educational and research. It is mostly cost-effective method for repurpose the old drug for new uses. We believe that Insilco approach is the most helpful in drug discovery. The drug repurposing studies must define by research centers, universities and pharmaceutical companies. The new indications for the known drugs are discovered. Traditional or denovo drug development strategies are expensive ventures. Drug re-purposing is powerful tool in drug discovery.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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