A REVIEW ON DRUG REPURPOSING FOR DIABETES EPIDEMIC

By

Sadia Raisa Lamia
17146029

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name &Signature:

Sadia Raisa Lamia
17146029

Approval

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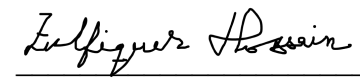
Examining Committee:

Supervisor:
(Member)


25.09.2021

Dr. Eva Rahman Kabir
Professor, Department of Pharmacy
Brac University

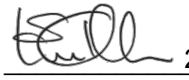

March 24, 2022

Dr. M.Zulfiquer Hossain
Associate Professor, Department of Pharmacy
Brac University

Program Coordinator:
(Member)

Dr. Zara Sheikh
Senior Lecturer, Department of Pharmacy
Brac University

Departmental Head:
(Chair)


25.09.2021

Dr. Eva Rahman Kabir
Professor, Department of Pharmacy
Brac University

Ethics Statement

This study does not involve any kind of human or animal trials.

Abstract

Repurposing of existing drugs to treat chronic, communicable and non-communicable diseases is becoming progressively important since it uses existing drug molecules or failed compounds by utilizing the available data. It uses several approaches, potentially decreasing the total development cost and shorter development timeframes. The traditional search for drugs for the treatment of diseases is a slow process, where significant expenses of new drug research and development are involved. This review discusses the drugs that are being approved for diabetes epidemic using drug repurposing approaches, as well as the challenges and future perspective.

Keywords: Drug repurposing, Diabetes, Antidiabetics, Clinical trials, Mechanism

Dedication

Dedicated to my parents

Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with strength during this whole period, I am indebted and would like to express my sincere gratefulness and gratitude to my supervisors Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy, Brac University & Dr. M. Zulfiquer Hossain, Associate Professor, Department of Pharmacy, Brac University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey. Last but not the least, I would like to take this opportunity to thank all those personalities who have helped me for all my educational achievements.

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List of Acronyms

T2D	Type 2 diabetes
DR	Drug Repurposing
CADD	Computer Aided Drug Designing
EMA	European Medicines Agency
FDA	Food and Drug Administration
WHO	World Health Organization
PPARG	Peroxisome Proliferator-Arouse Receptor Gamma
vHTS	Virtual High-Throughput Screening
HTS/HCS	High-Throughput and/or High-Content Screening
SRP	Signature Reversion Principle
GPCR	G-Protein-Coupled Receptors
GWAS	Genome Wide Association Studies
EHRs	Electronic Health Reports
FAERS	FDA Adverse Event Reporting System
CPRD	Clinical Practice Research Datalink
CCLs	Cancer Cell Lines
LDL-C	Low-Density Lipoprotein Cholesterol
FXR	Farnesoid X Receptor

IR	Insulin Resistance
VMH	Ventromedial Hypothalamus
DREL	Drug Repositioning Evidence Level
SAE	Serious Adverse Event
HR	Hazard Ratio
QR	Quick Release
MOU	Method-of-Use
NDA	New Drug Application
sNDA	Supplemental New Drug Application

Chapter 1

Introduction

The global burden of chronic diseases, like cancer, heart diseases, type 2 diabetes, chronic lung disease, chronic kidney disease, Alzheimer's is on the rise and as such, the search for affordable and alternate drugs for their treatment is of paramount (Centers for Disease Control and Prevention, 2019). Diabetes is considered to be one of the world's fastest growing disease. Roughly 463 million people have been suffering from this disease according to the International Diabetes Federation. Currently, 463 million individuals are living with diabetes in the world. By 2030, that number is projected at 578 million and by 2045 it would reach 700 million. The prevalence is greater in urban regions (10.8 percent) than in rural areas (7.2 percent). Similarly, the prevalence of this disease is higher in high-income nations (10.4 percent) than in low-income countries (4.0 percent). 50.1 percent of people with diabetes are found to be unaware that they have it. Impaired glucose tolerance was globally prevalent in 2019 and the percentage was 7.5 percent (374 million). It is anticipated to rise to 8.0 percent (454 million) by 2030 and 8.6 percent (548 million) by 2045 (Saeedi P et al., 2019).

Despite significant investments in traditional medicine pipelines by the different pharmaceutical firms, the development of new medications has failed to address the growing prevalence of Type 2 diabetes (T2D). Till date two drugs have been successfully repurposed for diabetes, and many more potential therapeutic molecules are still under investigation. Nevertheless, there are some challenges associated with drug repurposing, which need to be tackled well for the progress of drug development by repurposing (Turner et al., 2016).

Drug repurposing, which is also known as drug repositioning is a method applied to identify novel indications and applications of existing drugs which are FDA approved and are in use

clinically. Drug candidates with new pharmacological activity or therapeutic characteristics can be developed using this method. Moreover, by drug-repurposing discontinued drugs, drugs which are in experiment or failed drugs at the time of development can be established for novel therapeutic indications (TT & KB, 2004a).

Drug repurposing (DR) is a novel way of identifying drug compounds and targets that have been de-risked at the time of development stages which helps to speed up the total process so that the production time, effort and costs are less. It has decreased the drug discovery failure rate, leading to therapeutic breakthroughs (Osakwe & Rizvi, 2016). The technique of drug repurposing is used to enhance the success rate of medication development since the traditional process of drug discovery is an expensive and time-consuming procedure. This process outperforms the standard drug discovery processes in terms of time needed for the drug development, cost, efficiency, and risk of failure and potential candidates has already been evaluated in a number of clinical trials.

DR is an efficient method for revealing new targets and pathways in a less costly and safer manner (Pushpakom et al., 2018). However, repurposing of drugs has recently gained popularity due to its high success rate. Drug development has progressed commercially after it was discovered to have an off-target impact or the newly discovered on-target effect. There are numerous examples of existing drugs to have shown alternate therapeutic indications. Successful Computer Aided Drug Designing (CADD) techniques for the identification of repurpose able drug molecules are also being used (TT & KB, 2004a). This had led researchers to search for the identification of a number of potential drugs for a wide variety of diseases, such as diabetes.

Chapter 2 Aim

Understanding drug repurposing in the development of new anti-diabetic treatments.

Chapter 3

Methodology

Recent literature was extensively studied. Secondary data for the study was compiled from several journals endorsed by Nature, Elsevier, Springer and other distinguished journals. The different conventional therapies such as insulin and sulfonylureas, as well as the drugs repurposed or considered for repurposing have been discussed in this study. The study compiles the different computational approaches and the tools used in drug repurposing for an antidiabetic drug. It also outlines the challenges associated with drug repurposing. Specific topics of drug repurposing were omitted due to the vast quantity of research in this field. In an internet search engine, the search was done with specific exclusion criteria. The review did not include potentially relevant research results such as conference contributions, working papers, or books.

Chapter 4

Diabetes

Diabetes leads to micro and macro complications, including stroke, coronary artery disease, which leads to a short-ended life expectancy.

United Nations and WHO have thus focused on diabetes as a significant global health problem in light of the massive worldwide epidemic of this disease, which is arguably the most serious non-communicable global disease generated by an unhealthy contemporary lifestyle. According to experts, diabetes and cardiovascular illness are like two sides of the same coin when it comes to cardiovascular risk. People with diabetes are more likely to die from heart disease than those without, and vice versa.

Estimation of diabetes prevalence for 2019 and forecast for 2030 and 2045 are found in the 9th edition of the IDF Diabetes Atlas. Adults aged 20 to 79 are included in the estimations, which include type 1 and type 2 diabetes, both diagnosed and undiagnosed There are 463 million individuals aged 20 to 79 globally who have diabetes (9.3 percent of all adults in this age range). 79.4 percent of people reside in low- and middle-income nations, according to estimates.

Diabetes is a result of abnormalities in insulin production or insulin activity, marked by persistent hyperglycemia. Carbohydrate, lipid, and protein metabolic irregularities are the outcome of insulin's role as an anabolic hormone. It is believed that these metabolic anomalies are caused by low insulin levels and/or insulin resistance in target tissues such as skeletal muscles, fat, and to a lesser degree liver, at the level of insulin receptors, the signal transduction system, and/or effector enzymes and genes. The intensity of the symptoms is determined by the kind and duration of the diabetes. In the early stages of diabetes, some individuals are

asymptomatic, though found later to be significantly hyperglycemic. This is found especially in children with total insulin insufficiency may suffer from polyuria, polydipsia, polyphagia, and weight loss.

Diabetes is classified into several types:

- Type 1 diabetes is an autoimmune disorder. Mainly occurs when the immune system attacks and kills pancreatic cells which are responsible for insulin production. It is estimated that 10 percent of the diabetic patient suffers from Type1 diabetes.
- Type 2 diabetes is mainly caused by insulin resistance when body is unable to use the insulin to transport sugar into the cell thus the sugar level in blood elevates and causes hyperglycemia.90 percent of the diabetic patient suffers from type 2 diabetes.
- Prediabetic is a state when sugar level of blood is higher than normal but not high enough to be diabetic. This state can be prevented and sugar level can be managed by managing healthy life style.
- Gestational diabetes. This type of diabetes occurs during pregnancy when the placenta produces hormones causing insulin resistance and the blood sugar level is elevated.

  Diabetes insipidus, despite its similar name, is a rare illness that is unrelated to diabetes mellitus. Basically, in this disease condition kidneys excrete too much fluid from body

4.1 Treatment of Diabetes

In the case of type 1 diabetes, insulin is the major therapy. This helps to make the hormone; the body doesn't generate. The four most widely used insulins are Type 1, insulin aspart, insulin detemir, and insulin glargine. Their levels of productivity are distinguished by the speed at which they begin working and the duration of their effects.

On the other hand, people having type 2 diabetes and gestational diabetes, the blood sugar can be controlled through diet and exercise. However, medication is required to reduce blood sugar when lifestyle changes aren't adequate.

Table 1: Commonly used antidiabetics

Drug class	**Description**	**Generic name**	**Brand name**	**Reference**
Insulin	Insulin is a peptide hormone that is produced as a precursor to insulin (pro-insulin), and that undergoes to proteolytic cleavage to form insulin. Produced by pancreatic beta cell	Rapid acting insulin: 1. Insulin lispro injection, 2.Regular human insulin, 3.Insulin glulisine, 4.Insulin aspart, 5.Insulin lispro Short acting insulin: 1.Regular human insulin Intermediate acting insulin:	Admelog Affeza inhalation powder Apidra, Apidrasolostar Novolog, Fiasp, Fiaspflextouch Humalog, Humalog pen, Humalog Kwikpen Humulin R, Humulin R pen, Novolin R Humulin N, Novolin N	(*Insulin | FDA*, 2019)

Drug class	Description	Generic name	Brand name	Reference
		1.NPH(Human insulin isophane suspension) Long-acting insulin: 1.Insulin Glargine, 2.Insulin Degludec	Levemir, Toujeo, Toujeo max Tresiba Flextouch	
Sulfonylureas	These substances stimulate insulin secretion thus called insulin secretagogues.	First generation: 1.Tolbutamide, 2.chlorpropamide, 3.Tolazamide Second generation: 1. Glyburide, 2.Glipizide 3. Glimepiride	Tol-tab Diabinese Tolinase Diabeta, glynase Glucotrol, Glucotrol XL Amaryl	(*Diabetes Medicines DIABETES TIPS*, 2018)
Glinides	These are known as Insulin secretagogues	1.Repaglinide 2. Nateglinide	Prandin Starlix	(*Diabetes Medicines DIABETES TIPS*, 2018)
Biguanide	These are categorized as an insulin sensitizer. It helps to increase glucose absorption by decreasing insulin resistance	Metformin	Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet	(*Diabetes Medicines DIABETES TIPS*, 2018)

Drug class	Description	Generic name	Brand name	Reference
Thiazolidinediones	TZDs) are insulin sensitizers as well.	1. Pioglitazone 2. Rosiglitazone	Actos Avandia	(*Diabetes Medicines DIABETES TIPS*, 2018)
α - Glucosidase inhibitors	They are starch blockers, reduces post meal glucose level	1. Acarbose 2. Miglitol	Precose Glyset	(*Diabetes Medicines DIABETES TIPS*, 2018)
DPP-4 inhibitor:	They inhibits the DPP-4 enzyme and lowers blood glucose level	1.Sitagliptin 2.Saxagliptin 3.Alogliptin 4.Linagliptin	Januvia, Onglyza, Nesina, Tradjenta	(*Information on Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	FDA*, 2016)
Sodium glucose co-transporter 2 (SGLT2) inhibitor	This class of medicine reduces the blood sugar level by blocking the action of sodium glucose co-transporter2.	1.Dapagliflozin 2.Canagliflozin 3.Empagliflozin 4.Ertugliflozin	Farxiga, Invokana, Jardians Steglatro	(*Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors	FDA*, 2018)

FDA Approved Combined Drugs

Table 2 lists some of the FDA approved combined drugs for the treatment of diabetes.

Table 2: FDA approved combined drugs for diabetes treatment (Adapted from (*Diabetes Medicines DIABETES TIPS*, 2018; *Insulin | FDA*, 2019)

Brand name	**Combination**
Humalog Mix 75/25, Humalog Mix 75/25 KwikPen	75% insulin lispro protamine suspension+25% insulin lispro injection
Humalog 70/30	70% human insulin isophane suspension+30% human insulin injection
Humalog Mix 50/50, Humalog Mix 50/50 KwikPen	50% insulin lispro protamine suspension+50% insulin lispro injection
NovoLog Mix 70/30, NovoLog Mix 70/30 Flex Pen	70% Insulin Aspart Protamine Suspension+30% IsulinAspart Injection
Ryzodeg 70/30, FlexTouch	70% Insulin Degludec+30% Insulin Aspart
Humulin 70/30, Humulin 70/30 KwikPen	70% NPH Human Insulin+30% Regular Human Insulin injection
Novolin 70/30	70% NPH Human Insulin+30% Regular Human Insulin Injection
ActoPlus Met, ActoPlus Met XR	Pioglitazone + Metformin
Avandamet	Rosiglitazone + Metformin
Avandaryl	Rosiglitazone + Glimepiride
Duetact	Pioglitazone + Glimepiride
Glucovance	Glyburide + Metformin
Glyxambi	Empagliflozin and Linagliptin
Invokamet, Invokamet XR	Metformin + Canagliflozin
Janumet, Janumet XR	Metformin + Sitagliptin
Jentadueto	Metformin + Linagliptin
Kazano	Metformin + Alogliptin
Kombiglyze, Kombiglyze XR)	Metformin + Saxagliptin

Brand name	**Combination**
Metaglip	Metformin + Glipizide
Oseni	Pioglitazone + Alogliptin
PrandiMet	Metformin + Repaglinide
Xigduo XR	Metformin + Dapagliflozin

Chapter 5

Drug Repurposing for Diabetes

As already mentioned, among the chronic diseases, diabetes is one of the rapidly growing disease of the world. It can lead to serious pathological complications such as cardiovascular disease, retinopathy, and nephropathy. Thus, there is an urgent need for new preventive and therapeutic approaches to combat this disease. Despite the large amount of investment of pharmaceutical companies in the traditional drug discovery pipelines, improvement of new drugs has failed to keep up with the rising incidence of many diseases, particularly type 2 diabetes (T2D). Moreover, drug development from traditional methods takes a lot of time, and the failure causes severe financial loss as well. Safety of anti-diabetics is also a major concern in the development stage of new drugs. In 2010, the European Medicines Agency (EMA) recommended suspending the use ofAvandiaof GSK since it was found to be a potential cause of heart attack. Similarly in 2013, Aleglitazar from Roche, was terminated in its Phase III clinical trial because of concerns for heart failure, bone fractures, and gastrointestinal bleeding. Moreover, the new antidiabetic drugs that have passed the initial stages of clinical studies, are still under the observation of FDA and EMA for their safety and efficacy. The extensive time, effort, and investment required to develop and market new, safer, more effective and affordable antidiabetics has led to exploration of novel approaches with lower risk of failure and greater assurance of safety. Drug repurposing is one such promising approach (Turner et al., 2016).

5.1 Steps in Drug Repurposing:

The four main steps in drug repurposing are as follows:

1. Compound identification
2. Compound acquisition
3. Development
4. Registration

It is evident that drug repositioning takes less time to discover a new compound. Drug repurposing takes approximately 3-12 years and costs approximately 300 million dollars (Pushpakom et al., 2018). On the other hand, the traditional discovery of a new molecule to be commercially marketed as a drug usually requires a longer time to get the safety and efficacy profile of a new drug (Hughes et al., 2011). It costs around 12 billion dollars, and takes approximately 10-17 years to identify and develop a therapeutic molecule, with the clinical trials being time consuming and costly (Parvathaneni et al., 2019). The advanced science and technology and available data regarding the candidate drugs help to accelerate the DR process. Moreover, the chance of failure is very less in this process of getting a new compound once the

DR process is completed with diligence (Allarakhia, 2013; G. Jin & Wong, 2014). Moreover, the development of repositioned drugs saves time and money.

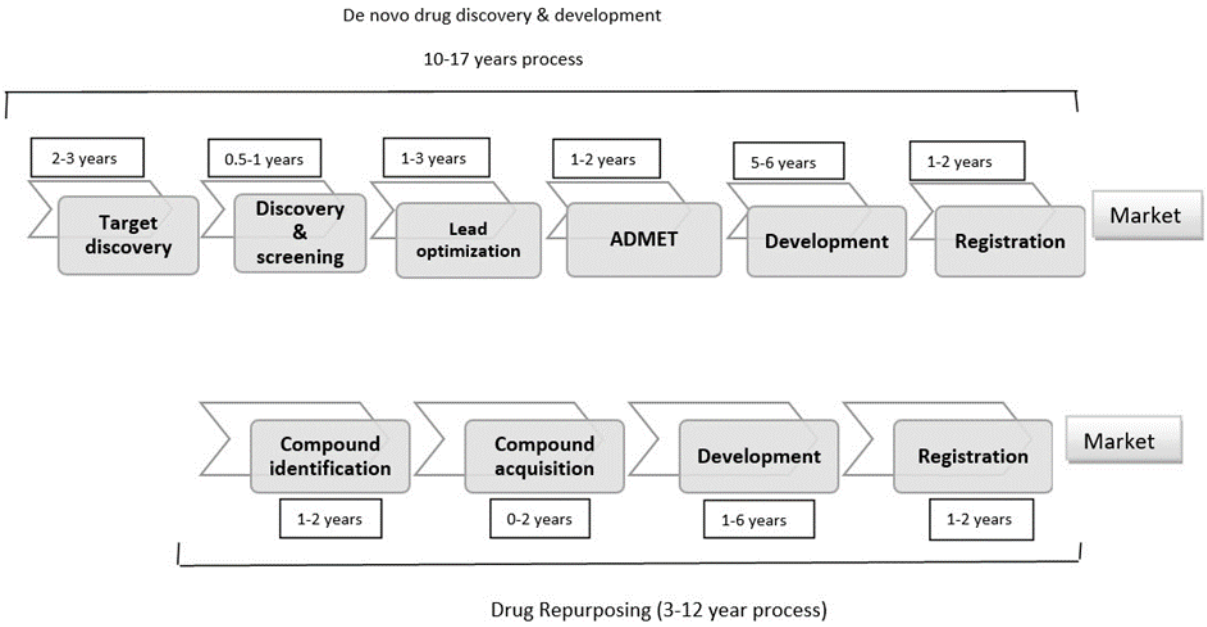

Figure 1: A Comparison between Traditional de Novo Drug Discovery and Development vs Drug Repositioning. Adapted from (TT & KB, 2004b).

5.2Strategies of Drug Repurposing:

On-target strategy and Off-target strategy are the main two Drug repurposing strategy. In On-target strategy, by using the existing mechanism of a therapeutic molecule novel indications are identified. The biological target of the therapeutic molecule stays same in this strategy but the disease is different (Ferreira & Andricopulo, 2016; Rudrapal et al., 2020). The pharmacological mechanism in the Off-target strategy, remains unknown. Drug and drug candidates act on novel targets and new therapeutic indications that were not previously considered. As a result, the targets and the indications both are new (Ashburn & Thor, 2004; Rudrapal et al., 2020).

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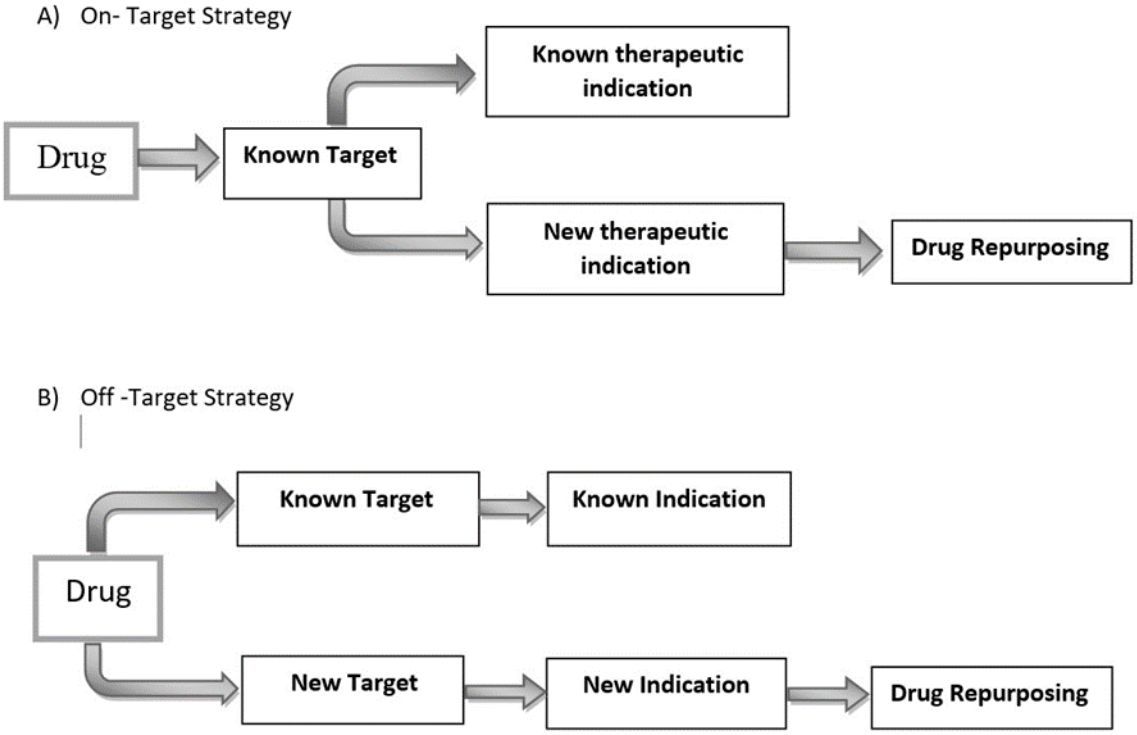

Figure 2: Strategies of Drug repurposing. A) On Target Drug Repurposing Strategy and B) Off Target Drug Repurposing Strategy. Adapted from (Vogrinc & Kunej, 2017)

5.3Approaches of Drug Repurposing

According to the availability of information relating to pharmacological, toxicological, and biological activity, in terms of quantity and quality the methods of DR can be divided into three major categories. These are:

i. Drug-oriented. In this process, properties of drug molecules such as adverse effects, structural characteristics, toxicities and biological activities are evaluated. Identification of molecules with biological effects that are based on animal or cell assays are done through this. In order to establish the biological efficacy of drugs, this methodology utilizes traditional pharmacology and drug discovery principles without the information of their biological targets. Such types of drug repurposing has been successful In this process, properties such as adverse effects, structural characteristics of drug molecules, toxicities and biological activities are evaluated. Identification of

molecules with biological effects that are based on animal or cell assays are done through this. In order to establish the biological efficacy of drugs, this methodology utilizes traditional pharmacology and drug discovery principles without the information of their biological targets. Such types drug repurposing has been successful

ii. Target-oriented. This category of repurposing approach involves the *in silico* screening or virtual high-throughput screening (vHTS) of drugs or compounds derived from drug libraries or databases of compounds such as molecular docking. This is followed by the in vitro (ligand-based screening) and in vivo (high-throughput and/or high-content screening (HTS/HCS) of drugs) steps against a selective protein molecule ora biomarker of interest. As opposed to a drug-oriented method, this method has a higher rate of success in drug discovery, because the disease pathways/mechanisms are directly represented by most of the biological targets.

iii. Disease/therapy-oriented: The availability of more information on disease model makes the application of the approaches relevant in drug repositioning. This category includes use of information such as genomics (disease specific genetic data), proteomics (disease specific target proteins), phenotypic data (pharmacological targets, off-target mechanism, pathological conditions, disease pathways, adverse and side effects etc.) and metabolomics (disease specific metabolic pathways/profile) regarding the disease process. Thus, it necessitates building of specific disease networks, recognition of expression of genetic profiles, consideration of key targets, identification of protein molecules that causes disease in the cell and metabolic pathways of the disease model.

5.3.1 Computational Approaches

In silico repositioning screens publicly available databases of huge chemical or drug libraries virtually by using tools such as bioinformatics or cheminformatics and computational biology

tools. This method identifies bioactive molecules which have the potential to be repurposed depending on the molecular interaction between the drug and protein target.

The computational approach has become very popular with a remarkable rate of success in drug discovery programs over the past few decades. Due to the abundance of information on chemical structures of bioactive compounds, proteins and pharmacophores in the public domain, a large number of drug discovery research laboratories and pharmaceutical companies have integrated the computational techniques and tools.

Computational approaches are mostly driven by data. They systematically analyze data of any type such as proteomic data, gene expression, chemical structure genotype or electronic health records (EHRs). These analyzed data can then pave the path to the formulation of repurposing hypotheses (Hurle et al., 2013). Computational approaches that are frequently used in drug repurposing are as follows.

- **Signature Matching:** This approach compares the distinctive or "signature" features of a drug with the unique qualities of another disease, drug or clinical phenotype (H. H et al., 2006; MJ et al., 2009). Three forms of data might be used to derive characteristics of a drug: proteomic, metabolomic or transcriptomic data proteomic, chemical structures; or profiles of adverse events. Comparison of drugs with disease (estimation of drug similarity – similarities with disease) and comparison of other drugs (drug similarity – drug similarity) is used for matching transcriptome signatures. In the first example, a particular drug having the transcriptomic signature might result from a comparison between the genetic profile of biomaterial, such as cell or tissue, before and after effect comparison of the therapy (F et al., 2013; JT, T, et al., 2011). Disease association gene expression is analyzed by the analysis of diseased condition against healthy condition then this is compared with the molecular signature of the drug. If the drug down regulates the upregulated gene in the disease condition, then the drug would be

considered as potential treatment of the disease. The degree of medication-related genes regulated up in the disease (i.e. a negative connection between the gene expression and medication's signature and that of the disease) would therefore enable us to determine whether or not this medicine may be a cure for the disease (JT, M, et al., 2011; S. M et al., 2011). This computational approach is based on the principle of signature reversion principle (SRP), when a drug reverses the expression motif of a certain set of genes characterized by a particular phenotype of the disease which is close to the healthy phenotype then the drug possibly could reverse the diseased phenotype itself. Even if this theory is simple, this principle is used for metabolic conditions and has been successful and has shown considerable effectiveness in the new drug repurposing prospects in a variety of therapeutic areas (S. E et al., 2015). By drug-drug similarity approach, similarity of pathways and mechanism of different pharmacological classes drugs can be identified and novel mode of action of a particular drug can be identified too. Moreover, by this principle, novel targets of existing drugs and off target therapeutic indications can be identified too. If two drugs show similarity of transcriptome signatures, they also have a therapeutic indication, even though the chemical structures differ (F et al., 2010).

Both methods of drug-disease similarity or drug-drug similarities include combining transcriptomic markers and relying significantly on data on gene expression that is accessible to the public. Nonetheless, another form of signature matching employed in the repurposing of drugs compares one drug with the other in order to recognize the existence of chemical similarities between drugs, therefore implying a common biological activity between these two drugs (TI et al., 2007). There are drawbacks of approaches to chemical similarity: physiological and chemical structures may have errors (JT, T, et al., 2011).

Last but not least, any drug's adverse effects profile may be utilized as a proxy for its phenotype. It is hypothesized that if these two drugs have the same adverse effects, they may operate in the same target or protein, or in the same pathway (JT, T, et al., 2011). The adverse effect phenotype of a specific drug can also be similar to the phenotype of a disease. This would imply that the physiology and pathway for this drug and disease are common (Pushpakom et al., 2018).

- **Computational Docking:** Molecular docking is a computational method based on structure that anticipates the interaction between a ligand such as a drug and a target like a receptor (DB et al., 2004). If information is available on a receptor target, various drugs can be explored for that target. This is called conventional docking. On the other hand, drug libraries can be utilized to identify a ligand for numerous targets. This is called inverse docking. Even with the advantages, this approach has some inconvenience. First, as pharmacological targets generally consist of several proteins, such as G-protein-coupled (GPCR) receptors, it is not always possible to achieve their 3D structures, although significant progress was achieved in GPCR crystallography (RM et al., 2015).

  Second, there is a challenge of getting correct structural information due to the lack of well-curated macromolecular target database sources (PS et al., 2014). Even though this can be overcome by the passing time and improvement (GL et al., 2006). Finally, it has been questioned about the efficacy of docking methods to predict binding affinity yet, although it's improving, differences may still be found across various software packages, and some prediction constraints are still there (NS et al., 2017; Pushpakom et al., 2018).

- **GWAS:** GWAS (Genome wide association studies) identify genetic variants of common diseases. These data further are used to identify disease biology, disease phenotype, novel targets which helps in drug repurposing (Sanseau P et al., 2012). But the use of GWAS

information for repositioning drugs is challenged, and its usefulness is now unclear. In gene-rich regions GWAS findings with high linkage imbalances can make In GWAS studies it can be challenging to identify causal and/or gene variants because GWAS signals in gene-rich regions with strong and might cause disequilibrium (Sanseau P et al., 2012). Another problem is the absence of data on the gene variant's direction of action; functional tests will need to be carried out to determine if the disease is controlled by an activator or suppressor. GWAS data do not provide comprehensive pathophysiological information, and therefore, before repurposing targets, doing a rational use of GWAS data is necessary (ZY & HY, 2013). It should also be mentioned that the human genome's present knowledge is not definitive, and many more novel genes might be found (W. C, 2018).

- **Pathway or Network Mapping:** Pathway based methods or network-based approaches have been utilized to discover drugs or pharmacological targets that might perhaps be repurposed (SB et al., 2012). As mentioned, while certain prospective targets identified by GWAS or by other methods may be immediately accessible, these genes might not be the ideal targets for pharmaceutical drug use. In certain instances, a pathway-based method might give information about genes downstream or upstream of the GWAS-related target which can be used for repurposing opportunity (CS & BF, 2016). On the other hand, network analysis includes building networks of drug/disease based on patterns of gene expression, disease pathology, protein interactions and GWAS data to help identify potential drug repurposing applicant. To efficiently identify potential drug repurposing candidate network-based approach and GWAS are combinedly done in some experiments and shows better result (Pushpakom et al., 2018).

- **Ligand Based Approaches:** The idea that similar compounds have similar biological features is used for ligand-based methods. These approaches are widely utilized in the field of drug repurposing to assess and predict ligands' activities for new targets. Bioactive public databases

like DrugBank, ChEMBL and PubChem contain information that has been collected from literary data (G. A et al., 2017; DS et al., 2006; W. Y et al., 2017). These databases contain an enormous and ever-growing stock of biological and chemical data, such as binding affinity, cellular function, and Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties. This information is used for comparing similarity and the activity of potential drugs for repurposing. Moreover, recent progress in drug repurposing has included the publication of repurposed pharmaceuticals, failed drugs, and therapeutic indications of these treatments and data on bioactivity (AS & CJ, 2017b; S. K et al., 2018). One benefit of the use of these drug repurposing techniques is the fact that the number of compounds that are publicly available (more than 100 million supplied alone by PubChem) is far higher than the number of placed protein crystal structures (under 150,000 now in Protein Data Bank) (HM et al., 2000; W. Y et al., 2017). Ligand-based approaches, on the other hand, plainly depend on the chemical space coverage of the known compounds. Moreover, the great overall similarity does not always ensure activities on a secondary target (Stumpfe D & J, 2012). However, the rise in structural variety in biological databases will ultimately overcome this limitation (March-Vila et al., 2017; H. Y & J, 2013).

- **Retrospective Clinical Analysis:** A systemic strategy is now widely advocated for clinical data analysis to discover potential for drug repurposing (PB et al., 2012). Different sources, including clinical data, post marketing surveillance, Electronic Health Reports (EHRs), can be used to provide retrospective clinical evidence. EHRs include a vast number of structured and unstructured patient outcome data. The pathophysiological and diagnostic information, including the results of laboratory tests, and the prescription of medicinal products, is more structured. However, there are significant amounts of unstructured information such as clinical descriptions and imagery of patient symptoms that is important to define the phenotype of disease. This quantity of data in EHRs may be utilized to discover signals for repurposing drugs

(Karaman & Sippl, 2018). The vast number of EHR data also gives high statistical power. The United Kingdom Clinical Practice Research Datalink (CPRD), the European Medicines Agency (EMA) yellow card, the FDA Adverse Event Reporting System (FAERS), and the World Health Organization (WHO), global adverse drug reaction database (VigiBase) are important sources of data which can be used for further potential drug repurposing analyses. However, there are still considerable problems in obtaining and utilizing EHR data, including ethical and regulatory constraints limiting data access and making it difficult to extract unstructured information from the databases. The development of greater research capabilities in EHR databases can increase their usefulness for different downstream applications such as drug repurposing. Two additional major large data sources are post market surveillance data and clinical trial data. However access to these data might be restricted for commercial or confidential purposes. However, it is becoming increasingly clear that opening up access to this wealth of knowledge might contribute to future research into drug development and repurposing. In October 2016, the EMA started to provide direct public access to data from pharmaceutical firms provided by the clinical trials. This data may be utilized by academics and researchers for independent reanalysis and drug repurposing guidelines (Pushpakom et al., 2018).

- **Novel sources of data:** Cancer cell lines (CCLs) were utilized to assess their effects on cell survival in high-performance drug screens for hundreds of (both authorized and experimental) compounds (JN, 2012; YH & CR, 2016). Several studies have combined the pharmacological data sets produced by these screens with an extensive genomic characterization for the CCLs tested so that interactions between the molecular characteristics of cell and drug response may be identified (B. A et al., 2013; S.-L. B et al., 2015; F et al., 2016). It is a new resource to discover drug repurposing possibilities by using these data sets that are accessible to public combining linked genome and pharmacological data available on large panels of CCLs.

Naturally, CCLs are imperfect models: they might contain molecular changes that offer the *in vitro* culture selection advantages and could be biased towards specific molecular subtypes. However, despite these constraints, studies have demonstrated that assessing and identifying pharmacogenomic interaction helps to reiterate biomarkers which already exist in clinical use and by combining these data with clinical data will help to identify therapeutic genomic indicators. CCL studies also investigate genomic alterations of primary tumors based on clinical prevalence, and these vast data can be used further for drug repurposing (F et al., 2016). Of note, several of the novel pharmacogenomic interactions found were specific for tissue-type malignancies and involved medicines currently in clinical use in other diseases as well as in other tissue-type cancers. So, it is evident that data from such studies might be utilized in order to discover potential for repurposing drugs. Another frontier in speeding the repurposing research on drugs might be EHR-linked big DNA biobanks. Advances in sequencing technology allow enormous amounts of extensive genetic data from many people to be collected that might be beneficial for the repurposing of drugs, particularly for diabetes. However, the nature of large-scale data from these initiatives and from the usage of other high-performance technologies offers significant analytical problems as well as successful application, both in the discovery and repositioning of novel drugs (Pushpakom et al., 2018).

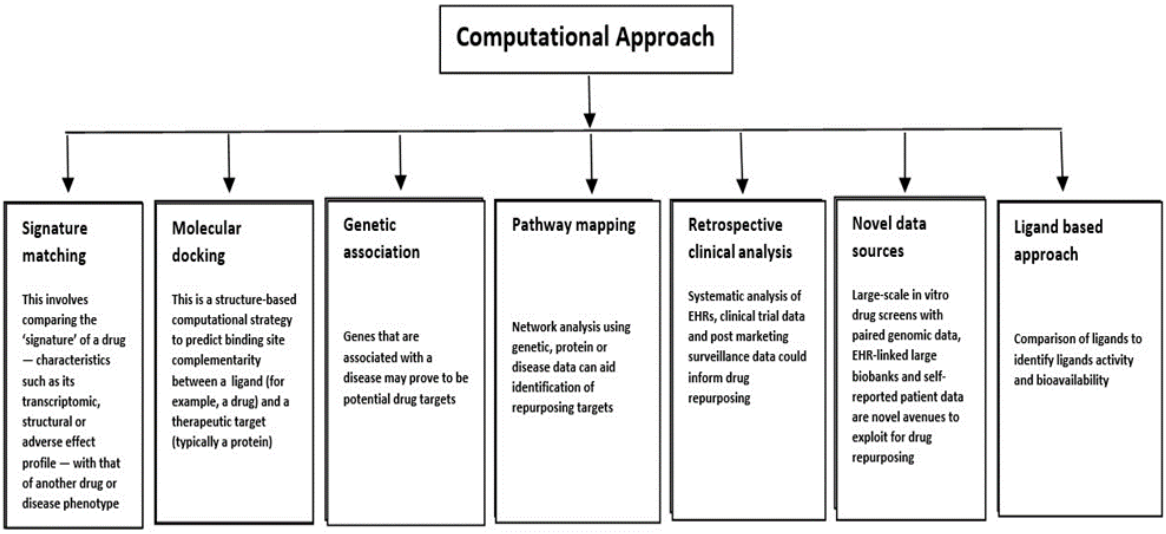

Figure 3: Computational Approaches of Drug Repurposing

Experimental Approach

The experimental approach is sometimes called activity-based repositioning referring to the screening of original drugs on the basis of tests and experimental assays for new pharmacological indications. This includes cell/organism-based and protein target-based screens in *in-vivo or in-vitro* models of diseases, without the need for any structural knowledge on objective of target proteins. Many experimental repositioning techniques are animal model, clinical approach, cell assay and target screening.

- **Binding Assay**

Binding assay is used to identify target interactions. Usually, proteomic techniques like mass chromatography and affinity chromatography are used. With this approach, binding targets and binding affinities of numerous drugs are identified. The drug-target stability is also assessed with this approach. For instance, when a compound binds with a target at its highest affinity, the thermal stability of the targeted protein can be determined by cellular thermostability assay (M. M. D et al., 2013). Moreover, by using chemical genetics, it gets easier to understand the relationship between therapeutic compound's binding and efficacy with their target and off-targets (DA et al., 2010; Pushpakom et al., 2018).

- **Phenotypic Screening**

Phenotypic screening can discover related to disease in model systems having no former understanding of the targets (JG et al., 2017). Phenotypic assays are tests that include cells or tissue collected from an experimental animal or people. Clinical observations and in-vitro–in-vivo models can be used to identify new drugs and new indications of approved drugs (Kim, 2015). For instance, it may include screening a chemical library against cell lines to observe cellular response; and identifying the compounds that effectively change the phenotype

followed by disease condition and mechanism of action (Lage et al., 2018). Robotic screening platforms and extremely sensitive detection devices are utilized to swiftly screen huge chemical libraries to discover new indications for approved drugs. The evaluation of a series of drugs in a variety of separate models with the goal of determining effectiveness in one or more of the evaluated models demonstrates the critical requirements for successful drug repurposing (Reaume, 2011; V et al., 2019).

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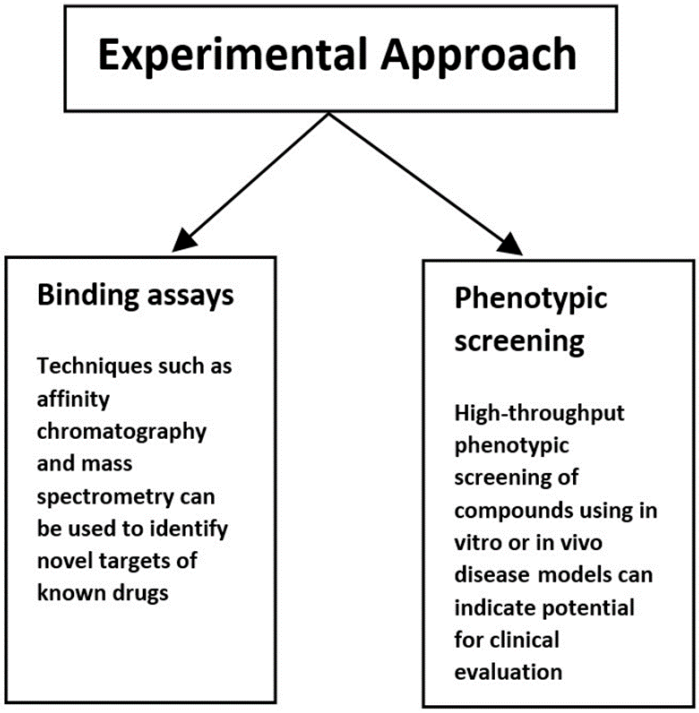

Figure 4: Experimental Approaches of Drug Repurposing

Nonetheless, *in silico* repositioning provides several advantages over the experimental-based approach, such as decreased development time and cost, as well as a low chance of failure.

Currently discovery scientists and researchers have used a hybrid strategy that combines *in silico* and experimental approaches to uncover novel therapeutic indications for existing drugs. The results of computational techniques are confirmed by pre-clinical biological investigations

(in vivo and in vitro trials) and clinical studies in the combined approach. The systematic use of computational and experimental techniques offers a rigorous and rational approach to the identification of novel indications, exhibiting better efficiency than serendipity-based discovery. Furthermore, the mixed approach allows for the development of repurposed drugs in a more efficient and timely manner. This method is both credible and reliable. Table 3 contains some of the commonly used disease and drug centric databases for drug repurposing.

Table 3: Commonly used Database for Drug Repurposing

Database	**Description**	**Reference**
ADReCS	System Toxicology and drug safety assessment *in silico.* 137,619 Drug-ADR pairings are given in this database.	(Cai MC et al., 2015)
ChEMBL	64 million chemical structures are stored in the database.	(G. A et al., 2012)
ChemSpider	A database of chemical structure, 6400 chemical structure included	(AJ, 2008)
Clue (L1000 Platform)	Dataset of human cell transcriptional responses to chemical genetic and chemical perturbation.There are 1.2 million L1000 tools and profiles for analyzing them.	(S. A et al., 2017)
Comparative Toxicogenomics Database	This database includes gene-disease, drug-disease drug-gene, and gene-gene associations.	(CJ et al., 2003)
DGIdb	Annotations of drug genes, interactions, and prospective drug abilities are stored in a database.	(G. M et al., 2013)
DrugBank	There are 11,000 medication entries in total, with each item containing chemical information and pharmacological targets of more than 200 fields.	(*DrugBank - PubChem Data Source*, 2021)
Drug-Central	Includes drug mechanism of action, chemical entities, indications, active ingredients, and pharmacologic information	(O et al., 2017)

Database	Description	Reference
e-Drug3D	e-Drug3D allows users to investigate FDA-approved medicines and active metabolites.	(P. E et al., 2012)
GDSC-Genomics of Drug Sensitivity in Cancer	Includes anti-cancer drugs screenings >1000 genetically defined human cancer cell lines	(Y. W et al., 2013)
Open Targets Platform	Includes robust and comprehensive data integration allowing access to and display of possible disease-related pharmacological targets	(K. G et al., 2017)
PharmGKB	A collection of genetic variations on curates' drug response	(H. M et al., 2002)
pkCSM	Prediction of small-molecule pharmacokinetic (ADMET) characteristics using SMILE data	(DE et al., 2015)
Project Achilles	A genome-wide database of tumor dependenciesto identify vulnerabilities linked with genetic and epigenetic changes.	(GS et al., 2014)
Promiscuous	The database includes three categories of entities - drugs, proteins, and the side effects and relationships between them.	(von E. J et al., 2011)
PubChem	PubChem includes the chemical information for over 90 million chemicals, as well as their bioactivities, protein targets and gene	(Kim S et al., 2016)
SIDER	Information about marketed medications and adverse drug reactions	(K. M et al., 2016)
STITCH	68,000 compounds, interactions, and over 1.5 million proteins in 373 species are recorded.	(K. M et al., 2008)
SuperPred	A website that predicts ATC codes and compound targets.	(D. M et al., 2008)
Therapeutic Target Database (TTD)	A dataset that gives the known and investigated therapeutic protein and nucleic acid targets, disease and pathway information, and the drugs directed at each of these targets.	(C. X et al., 2002)
Toxin and Toxin-Target	A database of 3673 toxins, that includedrugs, pollutants, pesticides, and food toxins, characterized by 41,733	(W. D et al., 2015)

Database	Description	Reference
Database (T3DB)	synonyms and connected to 2087 related toxin target records.	
Human Protein Atlas	It is composed of three parts, showing the distribution of proteins in all major organs and tissues of the human body.The Cell Atlas shows the subcellular localization of proteins in single cells, whereas the Pathology Atlas indicates the impact of protein levels on cancer patient survival rates.	(U. M et al., 2015)
KEGG Medicus	Database collection including information on genomes, chemical compounds, disease drugs and biological pathways.	(O. H et al., 1999)
Allen Brain Atlas	Maps of gene expression in the mouse and human brains	(S. SM et al., 2013)
ArrayExpress	Data about microarray gene expression at the EBI.	(P. H et al., 2005)
CCLE	Over 1100 cancer cell lines' mRNA expression and mutation data are stored in the database.	(B. J et al., 2012)
COSMIC	Catalogue of cancer-causing somatic mutations	(SA et al., 2015)
dbGAP	Catalogue of cancer-causing somatic mutations	(MD et al., 2007)
dbSNP	Single nucleotide polymorphism database	(ST et al., 2001)
dbVar	Public archives for genomic structural variation	(I et al., 2013)
DisGeNET	Human disease-associated genes and variants database	(P. J et al., 2015)
ENCODE	A comprehensive list of functional components in the human genome, consisting database.	(E. D et al., 2013)
Genomics Data Commons	Cancer Datasets Harmonized with 40 cancer mutated gene projects, 22,147 genes, and 3 million mutations	(RL et al., 2016)

Database	Description	Reference
GEO	Dataset of high-throughput gene expression	(T et al., 2005)
GTex	A list of genetic variants and their effects on gene expression.	("The Genotype-Tissue Expression (GTEx) Project," 2013)
Human Proteome Map	Massive peptide sequencing findings are available as an interactive resource.	(MS et al., 2014)
ICGC	Dataset including over 17,000 cancer donors from 76 studies and 21 tumor locations.	(J. Zhang et al., 2011)
IGSR	Data usability and expansion from the 1000 Genome Project	(C. L et al., 2017)
Orphadata	Rare diseases, drugs, and genes linked with them	(Aymé S & J, 2007)
Roadmap Epigenomics	Maps for stem cells and primary ex-vivo tissues selected to reflect the natural equivalents of tissues and organ systems commonly implicated in human disease.	(BE et al., 2010)
STRING	Protein-Protein Interactions, Networks, and Analysis	(Szklarczyk D et al., 2011)

Some commonly used tools and web-servers used in drug repurposing are listed in Table 4.

Table 4: Common tools and web-servers used in drug repurposing

Tool	Description	Reference
Clue	Used for searching for perturbagens (small chemicals or genes), L1000 cohorts, and heatmap display of gene expression	(S. A et al., 2017)

Tool	Description	Reference
Clue Repurposing Tool	Annotations on authorized and pre-clinical drugs can be accessed using an interactive application with this too.	(C. SM et al., 2017)
COGENA	Gene expression profile analysis, visualization, and grouping tool	(Z et al., 2016)
DeepChem	Toolkit for drug discovery and cheminformatics based on deep-learning	(A.-T. H et al., 2017)
DR.PRODIS	Used for predicting drug-protein interactions and adverse reactions	(Z. H et al., 2015)
e-LEA3D	Tools for computer-aided drug design	(D. D, 2010)
Frog2	Small compound 3D creation from 1D/2D input using a chemo-informatics toolbox	(MA et al., 2010)
GIFT	Gives drug-target interactions, infer chemogenomic characteristics	(Z. S et al., 2015)
GoPredict	Used for breast and ovarian cancer drug target prioritization	(R et al., 2016)
JOELib/JOELib2	A toolkit for converting chemical file formats, descriptor calculation classes, and substructure searching	(S. C et al., 2003)
ksRepo	Using gene expression drug datasets from diverse platforms, a method for repositioning drugs	(AS et al., 2016)
L1000CDS	Search engine for gene expression signatures based on the L1000 dataset	(D. Q et al., 2016)
MANTRA	Analysis and prediction of pharmacological mechanism of action in the context of repositioning	(C. D et al., 2014)
NFFinder	Used to identify genes that are up- or down-regulated can be used to find medications that are comparable.	(S. J et al., 2015)
Open babel	A chemical toolkit available for free	(NM et al., 2011)
Open PHACTS	An RDF-based data model for semantic integration of pharmaceutical data has been sponsored by the European Union.	(AJ et al., 2012)

Tool	Description	Reference
Biovista	Framework for discovering gene-protein interactions.	(A. C et al., 2011)
Alibaba	A tool for fitting a PubMed search as a graphical network.	(P. C et al., 2006)
ChemMapper	3D similarity (chemotype characteristics and molecular shape) calculating software.	(Gong et al., 2013)
ChemProt 3.0	Tool for identifying 2D similarity	(Taboureau et al., 2011)
HitPick	Tool used for 1NN similarity search	(Liu et al., 2013)
iDrug-Target	Tool that uses Fingerprint-based approach with machine learning	(Xiao et al., 2015)
Polypharmacology Browser (PPB)	Tool that uses multi fingerprint-based approach. Ten different fingerprints	(Awale & Reymond, 2019)
Similarity ensemble approach (SEA)	Tool that uses 2D similarity-based approach	(MJ et al., 2007)
SwissTarget-Prediction	Combination of 2D and 3D similarity approach	(G. D et al., 2014)
TarPred	KNN-based data fusion with 2D fingerprint-based similarity	(L. X et al., 2015)
TargetHunter	Tool that uses 2D similarity-based approach	(W. L et al., 2013)
idTarget	Divide-and-conquer-based docking approach	(JC et al., 2012)
PDID	Predictions generated using ILbind, SMAP and eFindSite	(K. A et al., 2006)
TarFisDock	Reverse ligand-protein docking approach	(L. H et al., 2006)
Balestraweb	PMF method	(Cobanoglu MC et al., 2015)
CSNAP	Tool that uses CSN-based approach	(Y. Y et al., 2010)
DASPfind	Tool that uses Network-based approach	(B.-A. W et al., 2016)
DT-Web	Tool that uses Recommendation-based approach	(Alaimo S et al., 2015)

Tool	Description	Reference
PROMISCUOUS	This tool has a new network-based approach to target–target and drug–target interactions as well as side effects in the works.	(von E. J et al., 2011)
SLAP	Tool for prediction using Semantic Link Association	(Chen B et al., 2012)
ProBis	The Fast Maximum Clique Algorithm tool.	(K. J & D, 2012)
PoSSuM	All-pairs similarity finding tool	(I. J et al., 2015)
DrugE-Rank	Tool that uses feature-based and similarity-based approach	(Y. Q et al., 2016)
SPiDER	Self-organizing map-based prediction tool	(R. D et al., 2014)
MeSHDD	Tool to find drug– drug similarity	(AS & CJ, 2017a)
RE:fine drugs	Tool to findgene disease interaction and drug–protein interaction	(M. S et al., 2016)
CMap	Tool for identification of gene expression profiles that are associated with drug sensitivity	(S. A et al., 2017)
DeSigN	Global baseline DEGs to drug response	(BK et al., 2017)
PDOD	Tool to predict drugs with opposing effects on disease genes	(Y. H et al., 2016)

Chapter 6

Drugs for Treatment of Diabetes Epidemic

6.1 Drugs Approved by FDA

The following section discusses the two FDA approved repurposed drugs that can be usedin the treatment of diabetes.

1. Colesevelam (Brand name Welchol)

It is a bile sequestering agent. It was mainly used for hyperlipidemia to decrease the increased level of low-density lipoprotein cholesterol (LDL-C). Colesevelam is now repurposed for type-2 diabetes mellitus. It got FDA approval in 2008 as anti-diabetic.

The mechanism of colesevelam to decreases blood glucose levels in patients with T2DM is unknown. However, there is growing evidence that bile acid sequestrants' glycemic effects are mediated by fibroblast growth factor-19, liver X receptor, farnesoid X receptor (FXR/bile acid receptor), and TGR5-mediated effects on intestinal glucose absorption and/or hepatic glucose metabolism, as well as effects on peripheral insulin sensitivity, incretin effects, and energy homeostasis. The gene expressions required in gluconeogenesis, such as phosphoenolpyruvate carboxy kinase and glucose-6-phosphatase, has been demonstrated to be reduced when FXR is activated by bile acids. FXR may also influence hepatic glucose synthesis while fasting and hepatic glucose utilization postprandially (D.-S. D et al., 2005; Y. K et al., 2004; L. P et al., 2009). The effects of changes in the bile acid pool in T2DM on FXR activation are still being studied. Emerging evidence suggests that FXR modulators play a partial regulatory role in peripheral insulin sensitivity, implying that FXR may have a future role in the treatment of insulin resistance and T2DM (Cariou B et al., 2006; M. K et al., 2006; Z. Y et al., 2006). Bile

acids have been demonstrated to increase glucagon-like peptide-1 (GLP-1) secretion via the G-protein-coupled receptor TGR5 activation, suggesting that they may influence incretin release (T. C et al., 2008; Katsuma S et al., 2005). Despite these gains, more research is needed to establish the exact mechanism underlying bile acid sequestrants influence on glucose metabolism in T2DM patients (Fonseca et al., 2010).

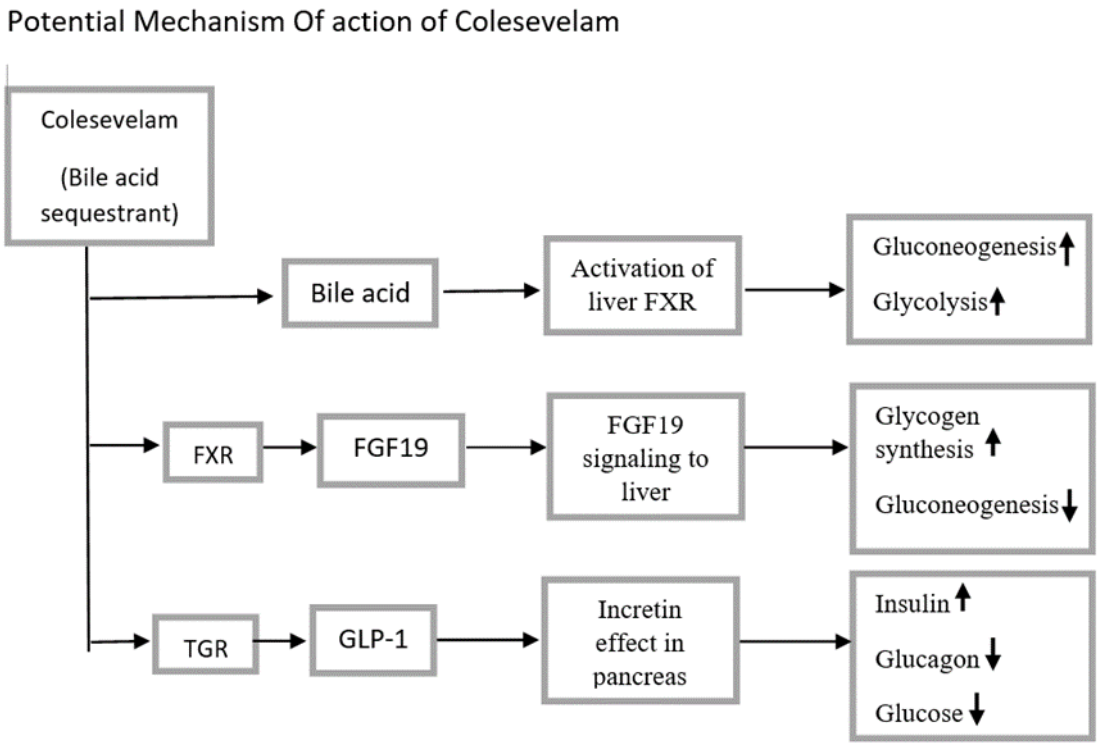

Figure 5: Potential Mechanism of Action of Colesevelam for Diabetes. Adapted from (Ramírez-Pérez et al., 2017).

Signature matching (Drug-drug) were used in the early development stage for repurposing colesevelam. Colesevelam was compared with first generation bile acid sequestrants. Afterwards, clinical trials and other experimental approaches were used in the process of repurposing.

Table 5 contains the summary of all the clinical trials of colesevelam carried out to date.

Table 5: Clinical trials of Colesevlam

Study	**Patient Disease condition**	**No. of participants**	**Age and gender eligibility**	**Treatment and duration**	**Result**	**Reference**
Study 1	Type 2 diabetes	316	All gender 18-75 years	Colesevelam hydrochloride metformin For 26 weeks	Lowered HbA1c level compared to placebo (-0.54%) Lowered Hba1c(-0.62%) by combination with metformin Lowered plasma glucose level (13.9 mg/dL)	(Bays et al., 2008)
Study 2	Type 2 diabates	461	All gender Age:18-75 years	Colesevelam hydrochloride with sulfonylurea And placebo For 26 weeks	Lowered A1c from baseline (-0.32%), and increased in placebo(0.23%) Lowers LDL cholesterol	(Fonseca et al., 2008)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment and duration	Result	Reference
Study 3	Type 2 diabetes	287	All gender Age 18-75 years	Colesevelam and placebo For 16 weeks	Glycated hemoglobin level from baseline to week 16 was found to be -0.41% (0.07%) for the colesevelam-treated group, and 0.09% (0.07%) for the placebo group Reduced fating glucose level Reduced LDL cholesterol	(Goldberg et al., 2008)
Study 4	Type 2 diabetes	236	All gender Age:10 to 17 years	-Colesevelam in high dose -Colesevelam low dose For 52 weeks	HbA1c ≥0.7% or ≥0.5% from baseline, and/or reduction in FPG ≥30 mg/dL from baseline	(*Colesevelam for Children With Type 2 Diabetes - Full Text View - ClinicalTrials.Gov*, 2011)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment and duration	Result	Reference
Study 5	Type 2 diabetes	61	All gender Age:18-80 years	Drug: Colesevelam Drug:Sitagliptin For 12 weeks	Fasting glucose level reduced (-.8% mol/l)) for colesevelam treated patients and (-0.6%mol/l) reduced in combined therapy Fasting gluconeogenesis in colesevelam treated patient (0.2uol/kg) And (-0.3% umol/kg) in combined therapy Postprandial Endogenous Glucose Production in colesevelam treated patient (-0.1) and (-0.2) for combined therapy Reduced post prandial insulin, glucagon, postprandial GLP-1, fasting insulin compared	(FJ et al., 2007)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment and duration	Result	Reference
					to the combined therapy with sitagliptin	
Study 6	Type 2 diabetes	38	All gender Age: 35-70 years	Drug: Colesevelam, Placebo Metformin For 12 weeks	Increased Glp-1 in colesevelam treated group than placebo Decreased plasma glucose concentration, HbA1c level, insulin concentration in colesevelam treated	(S. G et al., 2013)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment and duration	Result	Reference
					group than placebo	
Study 7	Type 2 diabetes	357	All gender Age: 18 years and above	Drug: Welcol, placebo For 24 weeks	HbA1c decreased (0.41%) for welchol treated group and (0.14%) decreased in placebo treated Fasting plasma glucose decreases (-4.6mg/dl) and in placebo treated group it increased 5.7 mg/dl	(R. J et al., 2014)

2. **Bromocriptine (**Brand Name Cycloset**)**

Bromocriptine is a dopamine receptor agonist. Its main indication is hyperprolactinemia-associated dysfunctions, acromegaly and Parkinson disease. Bromocriptine was FDA approved in 2009 for treating type 2 diabetes.

While examining the metabolism of migratory birds, the idea of utilizing bromocriptine to treat type 2 diabetes arose. They exhibited seasonal variations in body fat storage and insulin sensitivity, according to the researchers. The temporal interaction of circadian neuroendocrine oscillations controls body fat storage and insulin activity in vertebrates. When food supply is scarce during hibernation, migration, and overwintering, many vertebrate species acquire obesity and insulin resistance (IR). The basal lipolytic activity accelerates during the shift to this insulin-resistant state, sparing glucose use by peripheral tissues and favoring fat oxidation

becomes predominant. During lengthy periods of winter food scarcity, hepatic glucose synthesis and gluconeogenesis increase to provide glucose to the CNS (RI et al., 2010). It's a tactic of their winter survival. Animals revert to the insulin-sensitive / glucose-tolerant phase towards the ending of the season and become slim. Dopamine levels are low when they are insulin-resistant, but they rebound to normal once they're back in the insulin-sensitive condition. In insulin-resistant animals, intracerebral bromocriptine treatment reduces increased VMH noradrenergic and serotonergic levels, resulting in improved insulin sensitivity and decreased plasma glucose and adipocyte lipolysis (AH et al., 1993; L. S et al., 1998, 1999b; M. Zhang et al., 2015).

Insulin resistance development in animals throughout these seasons of seasonal shift closely resembles the changes seen in people with type 2 diabetes and insulin resistance syndrome. Reduced hypothalamic dopaminergic tone may be implicated in the development of insulin resistance, according to research (Defronzo RA, 2011; DeFronzo RA & E, 1991).

Because of the ample calorie intake year around, the typical circadian cycle that results in a slimmer body in the summer and a heavier body in the winter is altered in humans, resulting in the lack of a lean phase. It's thought that type 2 diabetics experience a morning decrease in dopaminergic tone, which leads to greater sympathetic activity (Kalra S et al., 2011). Plasma prolactin concentrations in lean, normal, glucose-tolerant, insulin-sensitive individuals peak at night, during sleep (L. S et al., 1999a).

Insulin-resistant people had higher daytime plasma prolactin levels than non-insulin-resistant people, which is associated with lower dopaminergic tone. Bromocriptine mesylate, a sympatholytic dopamine D2 receptor agonist with inhibitory effects on serotonin turnover in the central nervous system, is an ergot derivative. Quick-release Bromocriptine, taken once a day, is thought to reset the circadian clock, which has been locked in a winter rhythm for a long time. This indicates that in insulin-resistant individuals, the excessively high hypothalamic

drive for increased plasma glucose, triglycerides, and free fatty acid levels is reset in fasting and postprandial states (Defronzo RA, 2011; Shivaprasad & Kalra, 2011).

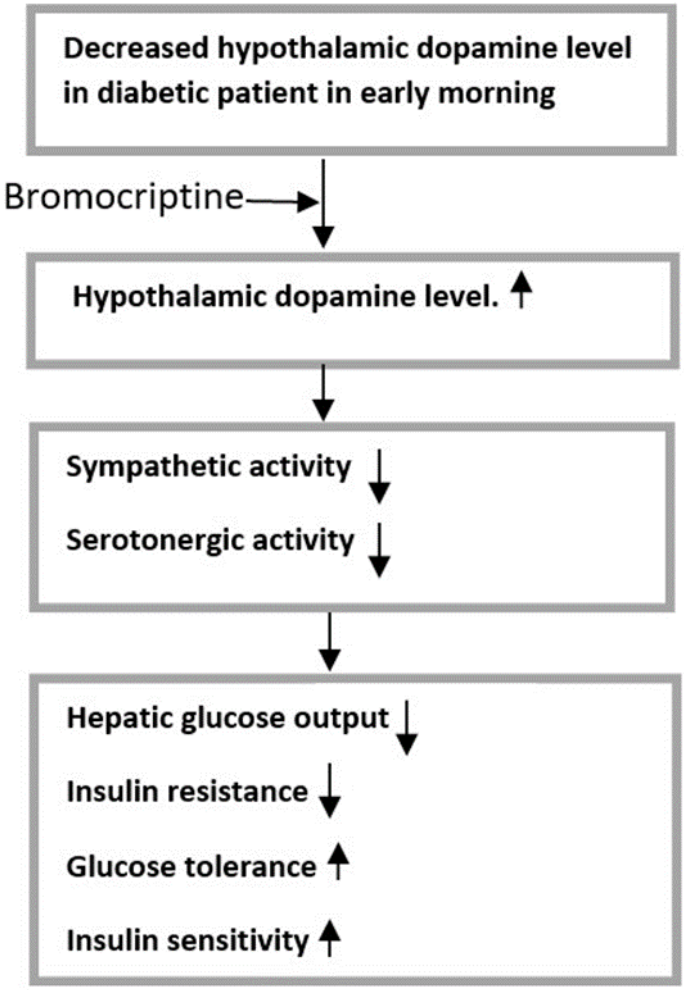

Figure 6: Potential Mechanism of action of Bromocriptine for diabetes. Adapted from (DeFronzo, 2011)

It was serendipitously discovered while studying hibernation of seasonal birds. Then other experimental models, phenotypic screening was used to identify the effect of Bromocriptine for glycemic control. Then pathway mapping for dopaminergic pathways was also done along with several clinical trials.Table 6 contains the summarized clinical trial results of Bromocriptine that have been carried out to date.

Table 6: Clinical Trials of Bromocriptine

Study	**Patient Disease condition**	**No. of participants**	**Age and gender eligibility**	**Treatment**	**Result**	**Reference**
Study 1	Type 2 diabetes	3095	All gender Age:30-80	Drug: Closet Drug: antidiabetics plus placebo For 52 weeks	In bromocriptine administered group 8.6% reported for severe adverse effect compared with 9.6% in placebo group. -some people reported CVD Nausea was the most reported adverse effect for bromocriptine group	(Gaziano et al., 2010)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment	Result	Reference
Study 2	Type 2 diabetes	15	All gender Age: 30-65 years	Bromocriptine with insulin and metformin For 24 weeks	In metformin+ insulin administered group HbA1c percentage was 9.47 and with bromocriptine it was 7.98 No severe adverse effect reported	(*QR-Bromocriptine as an Adjunct to Insulin and Metformin in the Treatment of Type 2 Diabetes - Full Text View - ClinicalTrials.Gov*, 2011)
Study 3	Type 2 diabetes	1791	All gender Age 30-80	Drug: bromocriptine Drug: Antidiabetics and placebo	CVD events occurred 1.3% in bromocriptine treated group And 3.1% in placebo treated group Glycemic control evaluated	(Chamarthi et al., 2016)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment	Result	Reference
Study 4	Type 2 diabetes	1834	All gender Age: 30 – 80 years	Drug: Bromocriptine Drug: placebo for 52 weeks	CVD endpoint reduced by 48% Showed good glycemic control	(Chamarthi et al., 2015)
Study 5	Type 2 diabetes	66	All gender Age: 18-75 years	Drug: Bromocriptine mesylate Drug: Placebo For 18 weeks	Bromocriptine treated group showed 0.95% decreased HbA1c and placebo administered showed 0.87%. (3.37%) reported severe adverse effect angina. And some other adverse effect were reported like nausea,v	(*Efficacy and Safety of Cycloset® Compared With Placebo When Added to Metformin - Full Text View - ClinicalTrials.Gov*, 2007)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment	Result	Reference
					omiting, blurred vision,back pain , dyspepsia etc.	
Study 6	Type 2 diabetes	17	All gender obese individuals	Drug: Ergoset Placebo For 18 weeks	Reduced body weight compared with placebo Improved glucose tolerance than placebo	(Cincotta & Meier, 1996)
Study 7	Type 2 diabetes	16	All genders	Drug: bromocriptine and placebo For 16 weeks	No change in body weight Bromocriptine reduced HbA1c level (from 8.7% to 8.1%) and fasting blood glucose level(from 190 to	(Pijl et al., 2000)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment	Result	Reference
					172 mg/dl) Placebo increased the variables	
Study 8	Type 2 diabetes	40	All gender 40-70 years	Drug: Bromocriptine and placebo for 12 weeks	No changes in body weight Bromocriptine reduced HbA1c level (from 9.9% to 9.5%) and fasting blood glucose level(from 10.96 to 9.6 mol/dl) Placebo increased HbA1c level, and fasting blood glucose level	(Aminorroaya et al., 2004)

Study	Patient Disease condition	No. of participants	Age and gender eligibility	Treatment	Result	Reference
					was unchanged	

6.2Drugs in the Pipeline for Approval

The table below (Table 7) lists the repurposing drugs for diabetes that are not yet approved by FDA.

Table 7: Repurposing drugs for Diabetes

Drug Name	Original Indication	Repurposing approaches	Reference	Phase of clinical trials	Clinical trials
Amlexanox	Oral aphthous ulcers	Signature matching, Genomic approach, phenotypic approach		Phase 2	(*Efficacy of Amlexanox vs. Placebo in Type 2 Diabetic Patients - Full Text View - ClinicalTrials.Gov*, 2013)

Drug Name	Original Indication	Repurposing approaches	Reference	Phase of clinical trials	Clinical trials
Berberine	Infectious diarrhea	Signature matching(drug-disease), Genomic, Pathway mapping, Phenotypic		Phase 3	(*Effects of Berberine Hydrochloride and Bifidobacterium in Diabetes Mellitus Prevention and Treatment - Full Text View - ClinicalTrials.Gov*, 2015)
BGP-15	Ischemia–reperfusion injury	Phenotypic screening		Phase 2	(Literáti-Nagy et al., 2014)
Bile acids	Primary biliary cirrhosis	Phenotypic screening, Pathway mapping		Phase 4	(Amori et al., 2007; Shima et al., 2018; Thomas et al., 2009)
Diacerein	Osteoarthritis	Signature matching, Phenotypic screening, Retrospective clinical analysis		Phase 3	(Cardoso et al., 2017)
Hydroxychloroquine	Malaria, rheumatoid arthritis	Retrospective clinical analysis, Phenotypic screening		Phase 4 (Pre-diabetes) Phase 1 (insulin resistance) Phase 2 (Type-2 diabetes with hyperglycemia)	(Wasko et al., 2015) (*Rediscovering Hydroxychloroquine as a Novel Insulin*

Drug Name	Original Indication	Repurposing approaches	Reference	Phase of clinical trials	Clinical trials
					Sensitizer - Full Text View - ClinicalTrials.Gov, 2014) (*Hydroxychloroquine Versus Pioglitazone in Combination Treatment for Type 2 Diabetes Mellitus - Full Text View - ClinicalTrials.Gov*, 2014)
Methazolamide	Glaucoma	Phenotypic screening		Phase 2	(Saporito et al., 2012)
MLR-1023	Gastric ulcers	Phenotypic screening		Phase 2	(Lee et al., 2020)
Salicylates	Pain and inflammation	Phenotypic screening		Phase 2	(Goldfine et al., 2008)
TUDCA	Cholestasis Alleviates	Phenotypic screening		N/A	(Kars et al., 2010)
Triterpenoids	Anti-inflammatory, antipyretic, analgesic	Molecular docking, binding assay, Phenotypic screening		Phase 2	(*Effect of Ursolic Acid Administration on Insulin Sensitivity and Metabolic Syndrome - Full Text View - ClinicalTria*

Drug Name	Original Indication	Repurposing approaches	Reference	Phase of clinical trials	Clinical trials
					ls.Gov, 2014)
Verapamil	Hypertension	Genomic studies, phenotypic screening		Phase 2	(Ovalle et al., 2018)
Naltrexone	Opioid Addiction	Phenotypic screening		Phase 3	(Hollander et al., 2013)
Ustekinumab	Plaque Psoriasis	Pathway mapping, Phenotypic screening		Phase 2	(*Study of Tolerability and Safety of Adding Ustekinumab to INGAP Peptide for 12 Weeks in Adult Patients With TD1 Melitis - Full Text View - ClinicalTrials.Gov*, 2015)
Piroxicam (NSAID)	Osteoarthritis, rheumatoid arthritis	Molecular docking, Phenotypic screening,		Pre-clinical	(Chittepu et al., 2019)
Combination of Trolox C and Cytisine	Smoking cessation (Cytisine)	Signature matching my Cmap screening, Genomic studies, Phenotypic screening		Pre-clinical	(L. Jin et al., 2014)
Matrine	Hepatitis B	Molecular docking, genomic screening, phenotypic screening		Pre-clinical	(Zeng et al., 2015)

Drug Name	Original Indication	Repurposing approaches	Reference	Phase of clinical trials	Clinical trials
NEN	Intestinal infection with tapeworm	Phenotypic screening		Pre-clinical	(Tao et al., 2014)

6.2.1Drug Repurposing Evidence Level

According to the experts, the field of study of drug repurposing would be benefitted if there is clearer definition present in the articles or published papers. Therefore, based to the scientific evidence level, the categorization system of the papers and projects are called - Drug Repositioning Evidence Level (DREL). which has been developed for different types of drug repositioning projects.

By the provided quality of scientific evidence, the drug repurposing levels are classified. The assessment identifies five stages of DREL 7. Experts believe that there will be less subjectiveness in evaluating projects by classifying drug repurposing and restoring efforts according to the five DREL levels. For example, although DREL-0 may seem controversial to some, facts should really be distinguished from by computational calculations until such a time when scientific proof advances to the DREL-1 project *in vitro*. In fact, many journal papers directed at the software and related community do not reveal experimental evidence. Similarly, in vivo (DREL-2) effects, or even in clinical circumstances (DREL-3) toxicity, may be restricted for those compounds functioning on extremely high in vitro concentrations (DREL-1). Such a categorization method can aid the community in swiftly evaluating the amount of advancement for every project when connected to specific initiatives, thereby mitigating increased social expectancies for rapid treatments if evidence does not justify it.

Table 8: Classification of Drug Repurposing Evidence Levels (Oprea & Overington, 2015).

DREL level	**Scientific evidence quality**
0	Included without any evidence
1	Includes in vitro studies and prediction of results in in vivo situation
2	Includes animal studies and hypothetical effect relevance in human
3	Incomplete studies in human with appropriate dose along with information like clinical effect, medical records, proof of concept etc.
4	There are well-documented clinical endpoints seen for the repurposed medication at dosages within the safety limits

Examples of DREL level are explained below.

i. DREL Classification = 0

M. Zhang et al conducted a diabetic drug repositioning study. In PubMed they looked for a literature by utilizing keywords such as diabetes, GWAS, proteomics. Further research includes sixteen GWAS, seventeen proteomics and eighteen metabolomics studies on diabetes. The Human Metabolome Database (HMDB) was utilized for the extraction of the names of enzymes and transporters relevant to protein diabetes from previous studies. Both data were used to build the Cytoscape network of metabolites-proteins. In addition, a Therapeutic Target Database (TTD) has been used to assess if the potential for drugs projection is there for a group of diabetic risk proteins.

Results have shown that at least one drug project is present in 108 of 992 proteins. Of the 108 proteins, 35 were approved clinically and did not have a demonstrated human toxicity. Twelve targets for protein, which were correlated with 58 drugs, had pathogenesis data that suggest

their therapeutic potential. Connectivity Maps (CMaps), a bioinformatics tool were used to discover functional relationships between diseases, genetic disorders and drug activity, nine drugs were reported eligible for diabetic repositioning by CMap study. Valdecoxib, diflunisal, niflumic acid, and nabumetone, has usual target which is prostaglandin G/H synthase 2 linked with type 1 diabetes

Idazoxan and phenoxybenzamine, targets adrenergic receptor alpha-2A. Diflorasone, d-cycloserine and perhexiline are all the remaining three drugs (M. Zhang et al., 2015).

ii. DREL Classification= 1

The purpose of this study was to find novel anti-glycation agents from current drug product. 4 type of in vitro assays were conducted for 18 drugs during this study which are *in vitro* BSA-MG assay,in-vitro BSA-glucose assay, DPPH free radical scavenging assay and in-vitro Fe+2 chelation assay. As a result, these 18 drugs, which were not previously known, were shown to be activated in protein antiglycation. GraphPad Prism-5.0, SoftMaxPro 4.8, MS-Excel software programs were used to evaluate the findings. The enzyme kinetics software EZ-FIT is used to calculate the value of IC50. Among the 18 drugs nimesulide and dihydrate of phloroglucinol have been shown to be effective inhibitors of *in vitro* protein glycation. Based on the data the it can be recommended that in nimesulide,the polyphenilic ring, in phloroglucinol dihydrate and the nitrobenzene moiety, may be shown to be responsible for its anti-glycation action As a result of the investigation, it was shown that several drugs available for the treatment of protein glycation-mediated problems in diabetes have anti-glycation activity. To improve anti-glycation treatment, they can also be utilized as gufor altering their structures (Rasheed et al., 2018).

iii. DREL Classification = 2

In the study, a computational drug repurposing scoring system was developed to determine viable drug combinations for diabetes. Using this technique, they speculated drug combinations that may be utilized to treat type 2 diabetes after presenting over 1,400 drugs for diabetes. The up/down genes associated with diabetes have been discovered. The Array Express database was used to find up- and down regulated genes in type 2 diabetes. As a consequence, they found 185 genes that were upregulated in type 2 diabetes and 278 genes were downregulated correspondingly. They obtained drug-induced deregulated genes from the CMap database. The number of gene deregulations by each drug in the disease was subsequently counted. Then, the significance of any pair of drugs that reverse the disease genes in their experiment was rigorously evaluated by taking a number of mice and made several groups containing 10-14 mice in each group and kept them in high fat diet to build insulin resistance. Moreover, they conducted the experiment by treating a group of normal mice with saline and diabetic mice group were randomly assigned to one of the five groups including insulin (group SI),combination of Trolox C and Cytisine (group STC), saline (group SS), Cytisine (group SC) ,Trolox C (group ST), which had been approved by the Animal Care Committee of the Peking University Health Science Center. They performed all the animal experiments in compliance with the “Guidelines for Animal Experiment”. Finally, the results indicated that Trolox C's and Cytisine's combination is beneficial for the treatment of type 2 diabetes, however none of these is effective alone. These findings show that the approach described might assist to detect combinations of drugs for any other disease condition (L. Jin et al., 2014).

iv. DREL Classification: 3

In this study, salsalate's effect on lowering of glycemia and insulin resistance was assessed as a possible pharmacological target for diabetes and probable mechanisms of action to validate

NF-kB. The Institutional Review Boards authorized protocols where they asked for consent form all the subjects. The subjects which did not have clear documents for being diabetic were tested with 75-g oral glucose tolerance test. Three independent investigations have been successively conducted with three separate patient cohorts. The first two studies have been conducted using an open label trial design of 2 weeks duration, one dosed at 4.5 g/d salsalate (1.5 g/d thrice daily) for the historically-useful dosage and durations to improve the level of glycosuria and another one dosed at 3 g/d (1.5 g/d twice daily). In the third trial, the effectiveness of this study was assessed at maximal dosage using a randomized, double-mask placebo-controlled 4-week experimental design. Open label trials showed decreased fasting and post-challenge glucose levels after 2 weeks of therapy, both high (4.5 g/d) and standard (3.0 g/d) doses of salsalate. The use of salsalate, increased glucose utilization by roughly 50% and 15% at high and normal doses and lowered insulin clearance for euglycemic hyperinsulinemic clamps correspondingly. Only at the higher dose, dose-limiting tinnitus occurred. In a third double-masked, placebo-controlled trial, its shown that 1 month of salsalate therapy, improves fasting and post challenge glycemia with a maximum tolerated dosage (not tinnitus). Free-circulating fatty acids have been decreased and in all treated patient's adiponectin increased. These findings show that salsalates enhance in vivo glucose and lipid homeostasis and support a therapeutic approach by targeting inflammation and NF-kB in type 2 diabetes (Goldfine et al., 2008).

v. DREL Classification=4

In this article, the 52-week cycloset safety test assessed the overall safety and cardiovascular safety of this novel type 2 diabetes drug and examined the randomized, double-blind, multicenter test. A total of 3,095 diabetic patients were randomized 2:1 to bromocriptine-QR or placebo therapy who is under usual antidiabetic medication.

The safety end-point was the incidence of any serious adverse event (SAE) with a hazard ratio (HR) noninferiority margin of 1.5. The frequency of cardiovascular disease (CVD) in a prespecify analysis was assessed with a modified intent-to- treat analysis and the frequency of events defined as myocardial infarction, stroke, coronary vascularization and hospitalized angina or cardiac insufficiency.

As a consequence of this, 176 (8.6%) in the bromocriptine-QR group reported SAEs compared to 98 (9.6%) in the placebo group (HR 1.02 [96 percent one-sided CI 1.27]). In the bromocriptine-QR group fewer patients reported a CVD-ending point compared the placebo group (37 [1.8%] vs. 32 [3.2%], respectively) (HR 0.60, [95% two-sided CI 0.35–0.96]). In the bromocriptine-QR groups, nausea was the most often reported adverse effect. Between treatment arms, the frequency of SAEs was comparable. Fewer participants with bromocriptine QR have had a cardiovascular end point compared to individuals with placebo arm (Gaziano et al., 2010).

Chapter 7

Challenges

As previously stated, drug repurposing has had several notable successes. However, repurposing does not always work; certain drug candidates for repurposing may fail, usually during phase 3 studies. Some of the failures are unavoidable in later stage of development, as they are in the development of totally novel drugs, but toxicity should be less likely to be related with such failure because the candidates' safety profiles have already been characterized. Other causes for failure in the repurposing area (including lack of ability to begin to explore a potential candidate beyond initial investigations) are linked to obstacles of drug repurposing, as mentioned below:

- Dose adjustment: The right dose of a drug varies with its disease condition. For its maximum therapeutic efficacy, the recommended dose for a potential drug is important. Once a repurposed drug is licensed, clinical studies should additionally be done for an indication of its optimal dose.
- Heterogeneity and availability of data: In response to a rise in expression available to the public, open-source models were developed however access to some types of data is restricted to public, such as clinical data for patients, requiring substantial alteration for direct use and understanding. In addition, the heterogeneity of the data creates a further computational barrier for successful drug repositioning, integrating multiple variations of data like chemical structure, clinical data, and transcriptome data.
- Validation of Drug: To make drug-repurposing utmost successful, combining computational approaches for prediction and in-vitro confirmation is essential. Different drug repositioning approaches are used to detect new disease-drug connections and can be coupled with clinical records for effective drug determination like, electronic health records (HER), physical tests data, and information from health insurance. High-capacity in vitro or in vivo systems testing

of chemical products may be helpful in validating potent drugs anticipation. However, there is difference in in-vitro systems and in-vivo conditions mostly, for that validation should take into account in-vitro cell cultures that resemble in-vivo conditions.

- Patent considerations: To maximize the potential profit from repurposed products, it is important to protect the new indication by patenting it and defending the patent right. The ability to acquire patent protection may be limited if prior scientific knowledge of the repurposed usage cannot be distinguished from information already in the public domain. An applicant seeking patents for new medical uses will also be expected to provide in the patent application evidence that the medicine is a credible therapy for the new medical indications that are being sought. An MOU (new Method-of-use) patent can be obtained for an outdated generic medicine that has been repurposed. However, if the new repurposed indication relies on existing formulations and dosage forms of the generic drug, enforcement of MOU patent might be a big issue. Due to the fact that other manufacturers of the generic medicine may make it widely available, as well as the fact that physicians may prescribe it for non-patented purposes. As long as the generic manufacturer does not advocate the use of their product for the patented indication in any manner, it will be impossible to claim that they are infringing on the new MOU patent. To limit off-label usage of the newly-patent repurposed indication might be difficult in this situation, lowering the product's potential revenue.
- Regulatory Considerations: There is 10 years of market exclusivity in the EU/EEA for repurposed pharmaceuticals with recognized orphan indications, plus an extra 2 years if they are compliant with a Pediatric Investigation Plan (PIP). Each and every application for an orphan medication must be filed through the centralized process. Repurposed medicines without an orphan designation get 10 years of data exclusivity. In accordance with Article 10(5), applications for new indications of well-established drugs may be given a one-year data exclusivity. As a result, existing marketing authorizations that have been modified are not

subject to the data exclusivity clauses. FDA offers a three-year data exclusivity term in the United States for repurposing a previously-marketed medication, but this is not enough time for a firm to recoup the money it has committed. The off-label usage of a repurposed generic medicine may further devalue the product, as stated above in the section on patent issues.

- Organizational hurdles in industry: In the instance that the repurposed indication is not located within the organization's core disease area or the compound is no longer in development or been discontinued/terminated and thus no "live" project within the R&D division exists to provide dedicated support for the new indication. In other words, there are lacking of individuals and resources to carry out the research for drug repurposing (Pushpakom et al., 2018).

Chapter 8

Conclusion

Diabetes has risen dramatically in recent decades, indicating that present therapies are inadequate and new drugs and treatment options are urgently needed. Drug repositioning is gaining momentum as a valuable strategy for generating new candidates in addition to the currently used drugs. As previously stated, a number of drugs targeting pathophysiological pathways that impact glucoregulatory processes have been considered as potential treatments for diabetes through various approaches. More drugs can be identified with the better use of these approaches. Taking into account the opportunities and obstacles for drug repurposing described in the study, it can be concluded that drug repurposing is a promising tool to identify potential and novel treatments of diabetes. *In silico* results could possibly help in designing *in vitro* and *in vivo* trials in animals (insulin resistant mice, rodents etc.) The phenotypic screening results of *in vitro* models might differ from *in vivo* models. So, by performing more *in vivo* trials in animals which share similar phenotype with humans will help in finding clearer pathways, mode of action and effectiveness of the selected candidates.

Besides, as drug repurposing majorly depends on existing data of approved drugs, integrative systems for data analysis are required. Improvement in big data analysis will contribute to clearer identification of repurposing opportunities. In addition, clinical trials play an important role in drug repurposing for assuring safety and efficacy of the potential drugs. Several clinical trials get terminated for the lack of funding, so managing funds for clinical trials is essential. There is a need for clinical data access of industry-conducted clinical trials as well as data of safety trials of the potential compounds for academic researchers, which will help in further data analysis and research works.

Moreover, after repurposing the drugs, the safety liabilities with the new dosing schedule should be studied. This will ensure the safety of the drugs. Nonetheless, to make drug repurposing more convenient, measures should be taken to incentivize the challenges specially the patent and regulatory challenges. Changes in legislative and patent consideration will increase more opportunities for drug repurposing.

Finally, by mitigating all the challenges, drug repurposing can act as a promising tool in identifying alternative treatment options for diabetes.

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