DRUG REPURPOSING AND COMPUTATIONAL DRUG DISCOVERY FOR DIABETES

Abstract

The emergence of advanced molecular modeling software and speedy processing units has transformed the research of drug discovery in diabetes concerning type 2 diabetes mellitus (T2DM). This review highlights the recent advances and significance of *in silico* modeling for designing potential anti-T2DM drugs. The authors have discussed currently available information on the study of molecular modeling methods like molecular docking and drug repurposing for designing anti-T2DM drugs. Also, the authors have tried to present the limitations of *in silico* molecular modeling in T2DM drug discovery.

Keywords: T2DM; Drug Discovery; in silico Modeling; Drug Repurposing.

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I. INTRODUCTION

Diabetes mellitus is a metabolic disease recognized by high blood sugar levels over extended periods resulting in serious health problems. Hyperglycaemia is a symptom that identifies diabetes. It can harm pancreatic β-cell function and causes a reduction in the secretion of insulin. Thus, a vicious cycle of hyperglycaemia leads to an impeded metabolic state. Poorly controlled diabetes leads to severe consequences, causing harm to a wide range of the body's organs and tissues such as the heart, kidneys, nerves, and eyes. Diabetes is managed and diagnosed by checking glucose levels in a blood test.

After consuming oral carbohydrates, glucose (sugar) is produced during digestion. The insulin hormone induces glucose from the blood to be stored in the cells or utilized later for energy. With diabetes, either the body doesn't make sufficient insulin or can't effectively utilise the insulin it makes, or displays a combination of both. It is mainly categorized into pre-diabetes, Type 1 diabetes mellitus (T1DM), T2DM, and gestational diabetes.[1]

T1DM or insulin-dependent diabetes is caused due to autoimmune annihilation of the β-cells in the pancreas, resulting in absolute insulin deficiency. Whereas, T2DM is recognized by insulin resistance and the incapability to make enough insulin as shown in figure 1.

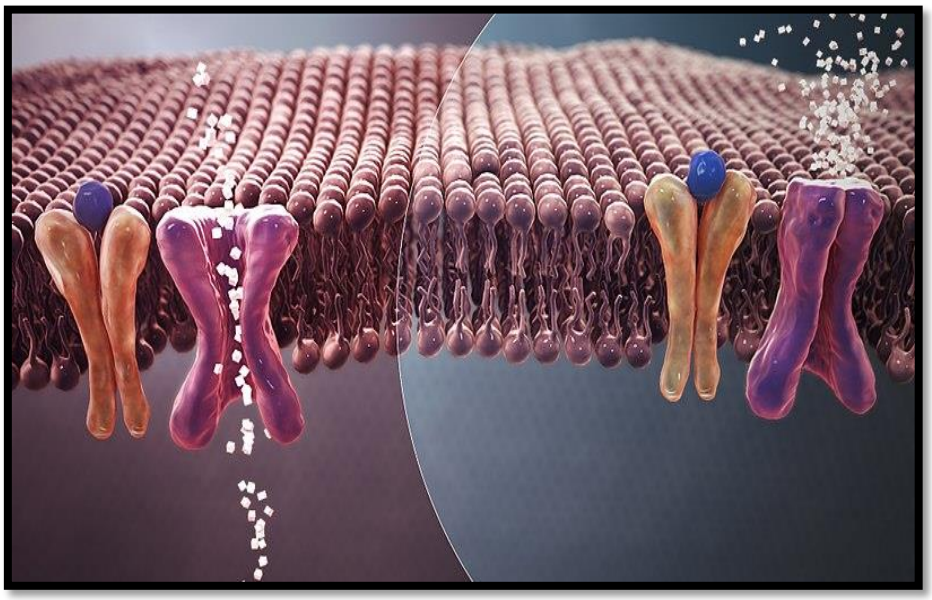

Figure 1: Mechanism of absorption of normal Blood Sugar Vs. insulin resistance in T2DM; Taken from [2]**, © Manu, licensed under CC BY-SA 4.0**

1. **Type 2 diabetes mellitus:** Resistance of insulin is multifactorial and commonly develops from aging and obesity. T2DM may induce a series of diseases including peripheral vascular disease, premature coronary heart disease, renal failure, stroke, blindness, and amputation[3],[4]. It is a chronic syndrome requiring long-term medication. Worryingly many of the accessible anti-T2DM drugs are facing limited tolerance and efficacy and exhibiting side effects[5],[6].

- **Global prevalence:** Since 1980, diabetes has prevailed approximately twice in an adult population. This shows a rise in risk factors like being obese or overweight[7]. Over the past decades, the prevalence of diabetes has expanded rapidly in middle- and low-income countries[8]. Diabetes bring about 1.5 million fatalities in 2012. High levels of blood glucose has given rise to an additional 2.2 million demises, by elevating the risk of cardiovascular disease and other disorders. 43% of 3.7 million demises occur before 70 years of age[9]. And in 2014, the average rate of the global prevalence of diabetes was around 9.2% as depicted in figure 2.

  It is approximated that around 462 million people are infected by T2DM, which denotes to 6.28% of global population. In 2017 alone, more than 1 million demises were attributed, ranking it as the 9th leading cause of mortality. Regarding human suffering, diabetes ranks as the 7th leading disease. To put this in perspective, in 1990 it was the 18th leading cause of deaths – the increase in risk is alarming[10]. The country-specified age-standardized pervasiveness of T2DM remained constant in 11 countries, reduced in 9 countries, and elevated notably in 119 countries[11]. Comparative research displayed a surging trend of the age-standardized pervasiveness of T2DM, but the rate of increase changes depending on the country, physical activity, education, and body mass index in the order of significance. Although numerous research has investigated the trends and prevalence of diabetes worldwide[12],[13], few studies have investigated the factors related to them.

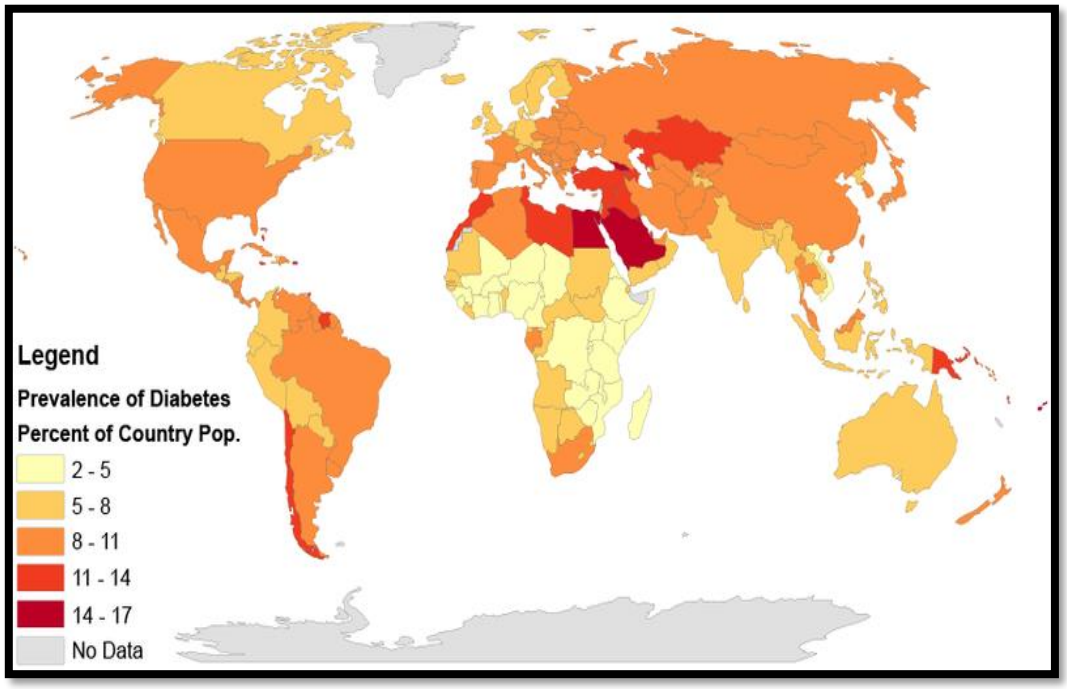

Figure 2: The Global Prevalence map of Diabetes in 2014 using data from 195 countries; Taken from [14]**, © Walter Scott Wilken, licensed under CC BY-SA 4.0**

- **Signs and symptoms:** The symptoms and signs of diabetes are commonly unnoticed because of the gradual chronic succession of the disease. People do not count it as a serious problem because unlike various other diseases, effects of hyperglycaemia are

not immediately manifested. The identification of early symptoms can aid to get this disease under control instantly and avoid possible vascular complications.

The classical symptoms of diabetes include polyuria, polyphagia, and polydypsia that usually arise in T1DM, and in T2DM also with severe hyperglycaemia. Serious weight loss is common in T1DM and in the case of T2DM, it remains undetected for a long duration. Common signs and symptoms include:

- weight loss
- often fatigue
- irritability
- regular infections
- frequent urination
- extreme hunger
- slow healing sores
- dry mouth
- burning, numbness, and pain on feet
- itching
- hypoglycaemia
- reduced vision
- dysfunction of erectile

- **Causes:** There exists no common cause of diabetes. They vary depending on the genetic makeup, environmental factors, family history, ethnicity, and health of the individual and also the type of diabetes. For instance, T1DM is an autoimmune problem where the pancreas is unable to produce insulin, whereas in T2DM the body is resistant to insulin.

  T2DM causes are usually multifactorial and are caused by several factors, such as lifestyle factors and genes. Genes can elevate the risk of T2DM by increasing the person's likelihood to become obese or overweight.

  - ***Overweight, obesity, and physical inactivity*** – People with limited physical activity are more prone to T2DM and are generally overweight or obese. Sometimes, the extra weight causes insulin resistance and cardiovascular diseases. The body weight can be frequently checked by body mass index.

  - ***Insulin resistance*** – T2DM generally begins with a resistance to insulin, a condition in which fat, muscle, and liver cells do not use the insulin well. As a consequence, the body requires more insulin to aid glucose entering cells. Initially, the pancreas makes enough insulin, but over time, insulin generation plateaus and the blood glucose levels rise.

- **Prevention and treatment:** The main goals of diabetes management are to attain better glycaemic control, avert macro and micro-vascular damage and alleviate symptoms. It is approximated that a 1% reduction in HbA1c results in a remarkable decrease in diabetes-associated deaths (21 %), a decrease in myocardial infarction (14%), and a decrease in micro-vascular complications (37%)[15].

- **Diabetes Education:** Education of diabetes is a vital job for a clinician. This disease is significantly affected by regular variation in infections, diet, exercise, and environmental stress[16]. Tips on physical hygiene, along with comprehensive guidance on dental care and foot, must be given. Also, intensive attempts must be taken to convince all diabetes patients to leave smoking as they might prone to debilitating retinopathy and vascular diseases. Exhausting exercise can cause hypoglycaemia and therefore diabetics should be educated to lower their insulin dose or adjust the carbohydrate content[17].

- **Exercise:** For diabetes, it is highly encouraged as a component of a therapeutic regime. Besides cardiovascular well-being, exercise also enhance glycaemic control. The useful impact on glycaemic control are produced from elevated tissue sensitivity to insulin[18].

- **Medical Nutrition Therapy:** It tailors the prescription of nutrition for diabetic patients depending on medical, personal factors, and lifestyle[19]. A well-balanced diet is the cornerstone of the therapy. High protein intake can cause continuation of kidney disease in diabetic nephropathy patients and so reduction in the protein intake is suggested. The diabetics must be guided to take fibres in their diet as they possess beneficiary impacts on cholesterol[20].

Figure 3: Exercise therapy for diabetes control; Taken from [21]**, © Sangudo, licensed under CC BY-NC-ND 2.0**

- **Weight Control:** Most of the T2DM cases are assigned to obesity and various diabetes-associated deaths. Only some T2DM patients can maintain and attain substantial weight reduction. Weight reduction pharmacotherapy can be efficacious in treating T2DM but is usually related to high dropout because of drug's adverse effects and so, is not advisable as fundamental treatment for the diabetes mellitus[22].

- **Bariatric Surgery for Obesity:** It is for individuals with body mass index >35 kg/m, particularly when diabetes is not controlled by pharmacologic therapy and lifestyle. This gastric surgery leads to continuous loss of weight and enhancement

in plasma glucose control. It results in near or almost complete normalization of glycaemia in T2DM patients, depending upon the surgical procedure[23].

- **Cardiovascular Risk Factor Management**: Besides glycaemic control, cardiac risk reduction includes the use of aspirin, smoking cessation, reduction in serum lipids, secondary prevention, and blood pressure control. These should be prioritized for all diabetic patients.

- **Vaccination**: Pneumonia, and influenza are the most common infectious disorders related to elevated morbidity and mortality in old age. Diabetic patients should take influenza and pneumococcal vaccination[24].

- **Psychological Assessment and Care**: Diabetes patients are more likely to develop mental health issues. This is in part due to the chronic nature of the disease, complicated medication regimes and anxiety and stress over complications – a condition commonly cited as "Diabetes Distress"[25], [26]. Social and psychological problems can impair a patient's capability to take care and might result in health issues. Thus, it's critical to evaluate psychosocial status timely and efficiently so that pertinent services can be made available[27].

- **Anti-Diabetic medications:** These are majorly of two types: injectable and oral. There are different classifications of oral anti-diabetic drugs possessing clinical impacts through a number of pathways. These drugs are routinely recommended worldwide and are very effective when employed lone or in association. Recent modalities for treatment emphasize on either increasing responsiveness, lowering the amount of glucose uptake or miming incretin effects, and elevating secretion of insulin. Metformin mono-therapy is considered the first-choice drug for all T2DM. Insulin is the very first option for patients with severe diabetic complications and acutely sick patients. Apart from this, glucagon-like peptide 1 analogues and di-peptidyl peptidase-IV (DPP-IV) inhibitors are relatively new inclusion to oral therapy, whereas thiazolidinediones (TZDs) and insulin sensitizers should be carefully exercised in people who are subjected to osteoporosis. Present drug modalities have shortcomings, but with advancements and technologies, there is a wish for great tomorrow for diabetes patients[28].

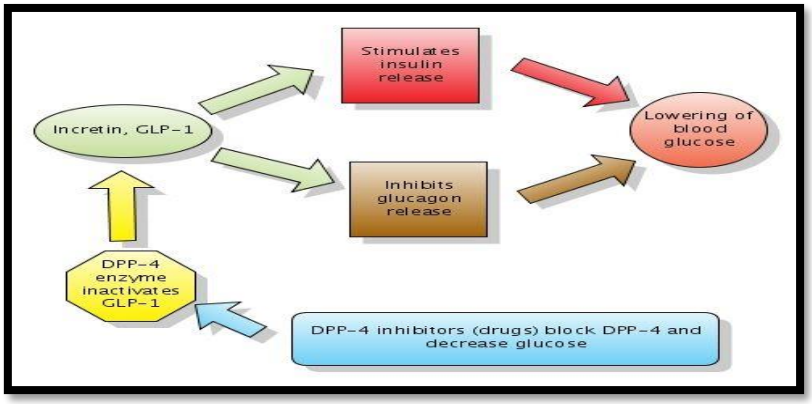

Figure 4: Action of incretins and DPP-4 inhibitors; Taken from[29]**, licensed under CC BY-SA 3.0**

2. **Problems and complications in anti-diabetic therapy:** There are various complications associated with diabetes treatment. Permeability and dissolvability issues are very common amongst the accessible anti-diabetes medications specifically sulfonylureas resulting in low bioavailability. Patients who respond with sulfonylureas initially, find resilience developing to the treatment over time. This necessitates in a periodic dose regimen, which causes patient's non-compliance and the higher possibility of dose skipping[30]. However, metformin which is recommended as the first-line treatment is greatly soluble but badly permeable resulting in very sedate and partial absorption[31],[32].

   Drawbacks observed with further anti-diabetes agents are short $t_{1/2}$ as observed in thiazolidinediones like pioglitazone leading to low therapeutic efficacy and poor bioavailability[33]. Another drug is repaglinide, which is recommended as an adjunct treatment. It possess a short $t_{1/2}$ and thrice-daily administration is needed often resulting in the non-compliance of patients[34]. Because of the severe gastrointestinal track's environment, insulin and a few other diabetic treatments like glucagon-like peptide-1 agonists display short $t_{1/2}$ and are administered via hypodermic pathways which leads anxiety to patients, injection site reactions which includes chances of infection, pruritus, itching, and local pain leading to poor compliance of patient[35]. This life-long exogenous medication can result in numerous shortcomings such as multi-insulin injections, problems in employing syringe method, self-injection, fear of painful injections, necrosis, potent dosing errors, damage of nerve, huge cost, infection, and issues at the injection site like the lipodystrophy[36]–[38]. Moreover, the traditional insulin replacement treatment is an 'open loop', which means it depends on the history of plasma glucose outline of the patient with reaction to several insulin treatments and meals in order to decide insulin doses. These medications can results in vomiting , gastric irritation, weight gain and nausea [39]–[42].

   Moreover, these treatments have limited tolerability, insolubility in water, limited effectiveness, high protein binding, gastric irritation, and episodes of weight gain and hypoglycaemia[43]. Furthermore, such therapeutic approaches don't permit natural glucose homeostasis and sometimes, cardiovascular complications might appear[44]–[46]. Thus, novel approaches are desperately required that stress on exploring and employing pathways which depends on physiological reactions and those which do not induce weight gain[47].

3. **Need for drug discovery of diabetes:** The shortcomings of injection remedy is overcome by managing the insulin levels while lowering the patient's burden[48]. Several devices such as glucose monitors and insulin pumps were introduced. Despite these technological developments, still there is a need for upgraded management tools[49],[50]. It remains hard to preserve the ideal level of glucose utilizing insulin replacement treatment in a wide range of people[51]. In a research, it was reported that approximately 50% of the patients with diabetes don't attain their targeted glucose level all through the day[52]. To attain these objectives, researchers are toiling to discover substitute pathways for administration of insulin[53], optimize pharmacokinetics of insulin and evolve novel therapeutic agents[54].

Early detection and subsequent disease management should be the priority. Although, in this concern, conventional testing techniques frequently fall short[55]. Traditional diagnostic methods such as analysing HbA1C levels, oral glucose tolerance tests, or fasting glucose levels, are considered agonizing by a few patients. They also depend on glucose measurements, which could change depending upon multiple factors, such as detection time, age, and some other physiological settings[56]. To describe the faults of conventional methods, several kinds of nano-materials were evolved to effectively manage diabetes[57]. Recently, nanotechnology has upgraded in numerous medical streams, like cardiology and oncology[58]–[61]. Indeed, the nano-scaled materials and nano-particulates possess several physical, biological and chemical effects which make them an interesting subject for medical studies[62]. The nano-materials are utilized to transfer both macro- and micro-molecular medications, and to detect and diagnose the progress of the disease[63]. Numerous nano-particulates has been created for applications in biomedical field, such as nanostructures, nanofabricated devices, liposomes, metallic nanoparticles, polymer nanoparticles, and stimuli-responsive nanoparticles[64]–[71].

The injectable and oral therapeutics are not very efficacious, specifically when the drug agent is a polypeptide that needs new delivery mechanics in order to reduce the adverse impacts[72]. As the effectiveness of the drug delivery has a direct relation with its size, nano-particulate formulations can improve the controlled release of drugs, improve bioavailability and allow more exact targeting of direct intracellular delivery[73]. A better comprehension of the pathogenesis of T2DM disease can be attained by concentrating on phenomenon like autophagy, genetic and epigenetic modifications[74]–[80]. The pathogenesis of T2DM, focusing on β-cells is determined as the promising therapeutic strategy anti T2DM. And in-depth investigation can result in the discovery of novel diabetic target points for future therapeutic interventions[81],[82]. The main approaches to designing anti-T2DM drugs are highlighted in figure 5.

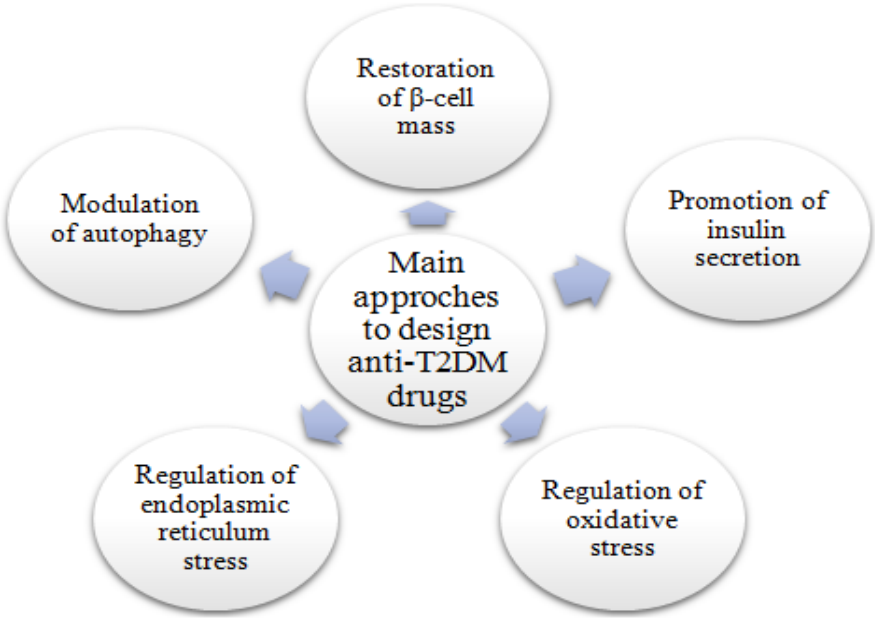

Figure 5: Main approaches to design anti-T2DM drugs

- **Drug Design:** Medications are very important for the treatment and prevention of any disease. Humans are continuously frightened by numerous disorders. So, ideal medications are always in high demand. The drug evolvement job is quite expensive, time-taking, challenging, and needs constant contemplation. To overcome these hurdles, various interdisciplinary strategies should be needed for the drug development procedure. A target of the drug is the biomolecule that is required in metabolic or signalling routes which is disease specific, for example, the receptor of the epidermal growth factor is very often altered or reformed. Biomolecules play vital roles in succession of a disease either by protein-nucleic acid interactions or protein-protein interfacing which results in the signalling action transfer and metabolic action alteration. Thus, change in biological roles are useful and can be achieved either by:

  - blocking the actions of biomolecules with tiny molecules which binds to the receptor site within the biomolecule, or
  - blocking the interactions of bi-molecule by tiny molecules to hamper cross-signalling betwixt the biomolecule, or
  - triggering the biomolecules for normal actions, which have been reformed functionally.

  Evolving an effective drug and a lead molecule is even strenuous for already recognized targets. Presently, discovery of a drug has considerably boosted because of the accessibility of 3D NMR or X-rays of biomolecules, the progress of in-silico techniques, and docking tools. The medicinal industry has growingly utilized contemporary pharmacy strategies, such as molecular modeling which is a strong tool to analyse structure-activity relationships (SAR). Both pharmacodynamics properties such as potencial, selectivity, binding affinity, efficiency; and pharmacokinetic factors such as excretion, distribution, absorption, toxicity, and metabolism are calculated by these strategies.

  The structure-based drug design (SBDD) technique gathers 3D structural data from biologic targets and is identified as an eminent element of contemporary pharmacy. Molecular dynamics (MD), molecular docking, and structure-based virtual screening (SBVS) are the commonly utilised SBDD techniques because of their vast variety of usage in the evaluation of molecular properties like binding energies, induced conformational changes, and molecular interactions. For ligand-based drug design (LBDD) technique ligand-based virtual screening (LBVS), generation of pharmacophore, Quantitative structure-activity relationship (QSAR) modeling, and similarity searching are employed. Both LBDD and SBDD methods are recognized as beneficial drug discovery mechanisms in academics as well as the industrial field, having their own synergy and versatility. The association of these methods were strongly used in several studies of biological, chemical, and structural data.

  A clear method in designing a drug includes utilisation of libraries of small biomolecule. The distinct diversity of chemicals in these libraries exhibits the interaction of ligands with a particular active site. The 3D structures of many vital targets and lead molecules remain unknown and unanalysed. Therefore an enhanced technique for designing a drug is very imperative to overcome issues related to presently accessible medicines.

- **Drug Discovery Cycle:** Drug discovery and designing is a repetitive process and usually progresses via numerous cycles before the lead molecule goes to clinical studies. The very first step comprises of cloning, structure determination, and purification of nucleic acid or the receptor protein by 3 main tools: homology modeling, X-ray crystallography, or NMR. It utilises in-silico fragments of molecules from a database, these molecules are ranked depending upon their connection with the respective active site. In the next step, the structural identification of the target molecule with the lead molecule which was identified in the first step, the in vitro micro blockage, and it also discloses other targets on the molecule which could be optimized further. Furthermore, it comprises of structural determination of new target in the lead complex, optimization of a lead compound, and synthesis of optimized lead[83]. After all the steps of drug discovery cycle, the optimized molecule generally display remarkable refinement in binding and is usually specific for the active site. Figure 6 illustrates the four-step cycle for associating computational efforts and structural information. A structure of the receptor of any form provides the starting point for modeling activities[84].

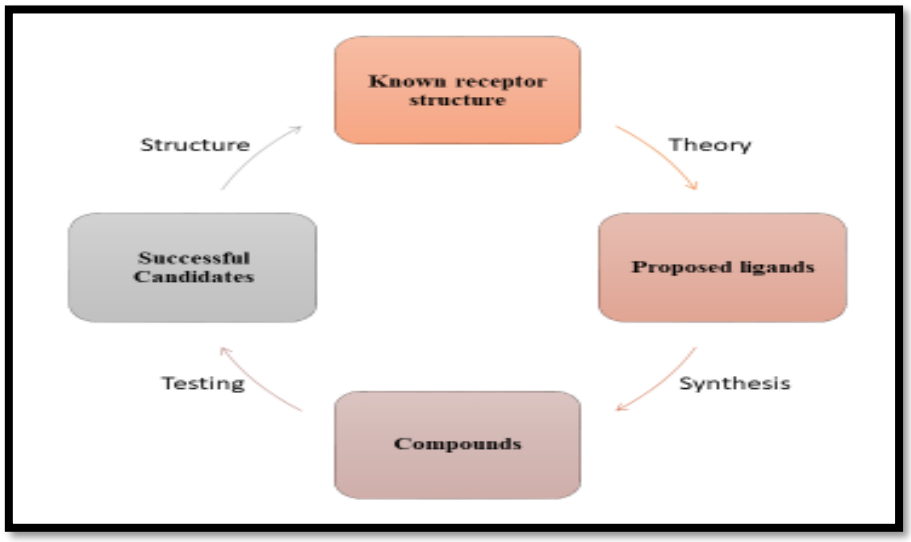

Figure 6: General approach to the drug design of biological inhibitors

4. **Role of drug repurposing and computational techniques for anti-diabetic drug discovery:** The traditional drug discovery methods are time-taking and costly techniques having a great possibility to fail. The advancement of cheminformatics/bioinformatics tools and availability of collected toxicological, pharmacokinetic, clinical, and safety data that are needed by drug repurposing approaches have remarkably reduced the cost as well as time of the drug development and also reduces the risk of failures in the clinical development. Recently discovery researchers and scientists have combined experimental and *in silico* approaches to recognize novel therapeutic indications for the existing drugs, which is called the mixed approach. The simultaneous application of experimental and computational methodologies in a defined manner offers a logical and robust approach to the invention of novel indications, exhibiting greater efficiency.

Recently, computer-assisted drug design approaches have made a huge contribution to the designing of new therapeutics[85]. Comparative Molecular Field Analysis (CoMFA) works by expounding the contour maps and provides new perception to design an inhibitor [86]. Also, the pharmacophore approach is very effective in drug design[87]. A pharmacophore model is a combination of electronic and steric factors which is required to check the supramolecular connections with the active site and to hamper its biological reaction. Virtual screening is another strong technique to introduce new hits[88]. Molecular docking is exercised to study the interactions of ligand and protein and to achieve biologically active conformers[89]. All these approaches are employed to discover novel inhibitors for T2DM.

Moreover, in drug designing, the electronic effects performs the main role [90]. Here, quantum chemistry calculations and docking studies are executed based on computational density functional theory (DFT)[91],[92]. Further, the novel hits are introduced with disparate scaffolds utilizing virtual screening, molecular docking, and ligand-based pharmacophore. Finally, toxicity and ADME prognostics were executed by virtual screening to procure the vital ADMET effects[93].

Recent development in high-throughput technequies, such as GWAS, microarray, and automation, ease the process of identification, diagnosis and remedy of expressed genes in any unusual situation. These genes are utilised as a sign for obstruction of any disorder[94]. Similarly, other databases like Gene Expression Omnibus (GEO), Array Express, and Sequence Read Archive also consists of high throughput sequencing detail. These details are re-analyzed employing advanced techniques and algorithms to get more remarkable data in contrast with the already published data. Before fetching any data, normalization and background correction of raw data should be instituted, employing the median and quadrantile regression techniques. But the median method may lose some information during the normalization of raw data[95]. Whereas, the quadrantile regression method, specifically "Robust Multiarray Average" (RMA) utilizes data from various microarrays. During calculation, RMA accounts for both well-behaved and apparent probes[96]. Also, the RMA technique yields the most reproducible results in contrast with the primitive median method[97]. Currently, a Gene Chip RMA is evolved, which is also known a (GC-RMA), which utilises sequence-specific probe affinities of the Gene Chip and transfers precise values of the gene expression. The GC-RMA is more potent than RMA as it considers the GC content of the probe during background correction.

By emphasizing the modern techniques of GC-RMA, recently a study was drafted to analyse the T2DM associated microarray datasets available in GEO database and T2DM gene information available in Genome-wide association study (GWAS) catalog for screening differently articulated genes in normal and diabetic case. Further, these screened genes would be used for characterization and identification of hub genes in T2DM and its related disorders employing STRING, WebGestalt, and Panther libraries. For novel drug discovery, these hub genes behave as possible targets in preventing T2DM and its related diseases[98].

II. DRUG REPURPOSING APPROACHES FOR ANTIDIABETIC DRUG DISCOVERY

Drug repurposing (drug repositioning) approaches aim at recognizing novel applications for already accessible therapeutics[99]. In discovering a novel therapeutic, drug repurposing has achieved a vital role, as it aids to circumvent optimization and preclinical evolvement problems, thus lowering failures, time, effort, and associated cost. The field of *in silico* designing of a drug is vast in which primary studies and practice motivate[100] and advance methods like combinatorial library design, QSPR/QSAR, cheminformatics, structure-based design, bioinformatics, and numerous chemical and biological databases are utilised. Moreover, many tools are available that offer a basis for designing inhibitors and ligands with desired specificity[101]. Various computational drug designing techniques which guide repurposing of a drug are discussed below:

1. **Comparative molecular field analysis (CoMFA):** CoMFA is a novel constructive technique that expounds the relationship of structure and activity. It is a 3D QSAR technique that delivers values of ClogP and describes the electrostatic and steric interactions of ligands[102].

   Homology modeling for protein is also identified as comparative modeling. This method generates a model of the "target" protein of unknown atomic resolution from its respective amino acid sequence and a pilot 3D composition of an associated homologous protein. Homology modeling comprises of the identification of recognized protein arrangements. It is noted that amongst the homologs, protein sequences are conserved less than protein arrangements, but the sequence structures vary with only <20%[103]. Research revealed that 3D protein composition is more conserved because the model of a target is generated by conserving the sequence using the template and sequence alignment[104]. As the protein arrangements are more conserved than DNA sequences, the identified sequence resemblance generally comprises of considerable similarity in structure[105]. Software of Modeller and Bioinformatics are utilized to create a 3D target structure based on known 3D structures of the templates[106]. The SWISS-model repository is the library of protein arrangements generated using homology modelling[107].

   Comparative molecular similarity indices analysis (CoMSIA) is another novel 3D-QSAR approach that is generally employed to identify the properties, necessary for proper binding of the receptor. It explores the electrostatic and steric interactions, hydrophobic areas, hydrogen bond donors, and hydrogen bond acceptors[108].

2. **3D pharmacophore mapping:** It is a simple, and powerful technique to swiftly identify lead molecules along with a favourable target. Traditionally, the pharmacophore is a 3D alignment of various functional groups in the molecular framework which are crucial during binding to the bioactive site of a target macromolecule or enzyme[109]. The prolonged techniques of QSAR studies modify pharmacophore details into the QSAR models which could be further utilized as screens for profiling of activity in virtual high-throughput screening method[110]. The chemical similarity exploration involves descriptor pharmacophores to create ingenious survey of virtual libraries or chemical databases to identify compounds possessing anticipated biological activities[111].

3. **Virtual high-throughput screening:** It is an in-silico technique that investigates huge databases to screen the compounds which are potent enough to bind with the active sites of the target compounds. To discover a novel drug, virtual screening is used to recognize those arrangements that would probably attach to the target molecule, generally an enzyme or a protein receptor[112]. According to Walters, et al. virtual screening is an "automatic investigation of huge datasets" utilizing a computational software[113]. It is faster than conventional screening, cheaper than High-Throughput Screening, and scans a huge potent drug-like compounds.

4. **Molecular docking (Interaction networks):** It predicts and visualises favoured adaptation of a molecule with another molecule to make a stable compound[114]. Molecular modelling/docking indicates binding of a ligand to a target protein or its receptor as shown in figure 7. It is employed to optimize and identify the drug agents by investigating the molecular properties between target and ligand biomolecules. It is also utilised to create various ligand orientations and conformations[115]. There exists numerous molecular docking software such as eHITS, DOCK, AutoDock, ArgusDock, FTDock, and FRED. Molecular modeling includes scoring tools which rank the ligands according to its binding affinity with the bioactive site. In high-throughput screening, various molecules were docked with their bioactive site, to determine their ranking with respect to their binding with the target biomolecule.

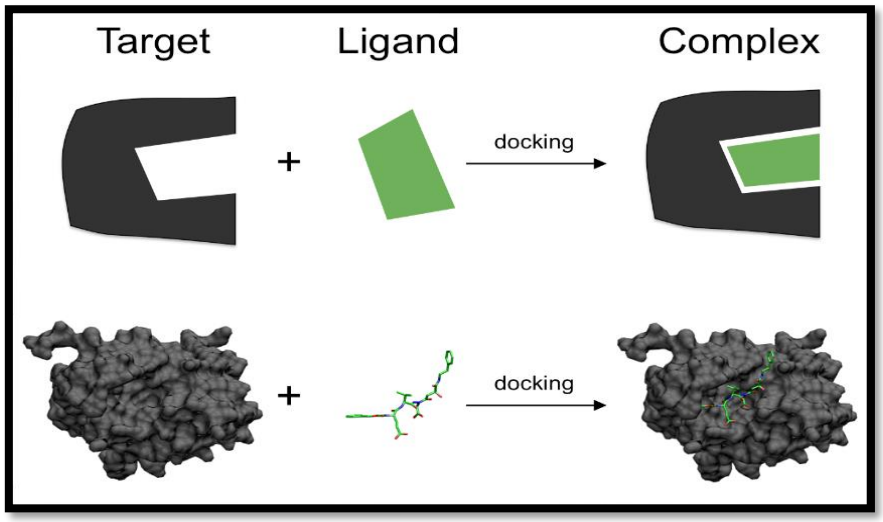

Figure 7: Schematic figure of docking a ligand (green) molecule with a protein (black) target forming a protein-ligand complex; Taken from[116]**, © Scigenis, licensed under CC BY-SA 4.0**

5. **Microarray analysis:** It is a DNA technology that performs a considerable role in the biotechnological advancement. Microarray studies help researchers to quickly comprehend various genes in a very compact sample and analyse the expressions of these genes. Figure 8 displays an appropriately arranged arrays of a known DNA sequence. Microarray studies possess applications in numerous domains, like cancer tissue microarrays, transgenic animal studies, and other diseases, normal cells, and tissues

during evolvement. This technique is employed to evolve potent and new drug agents[117].

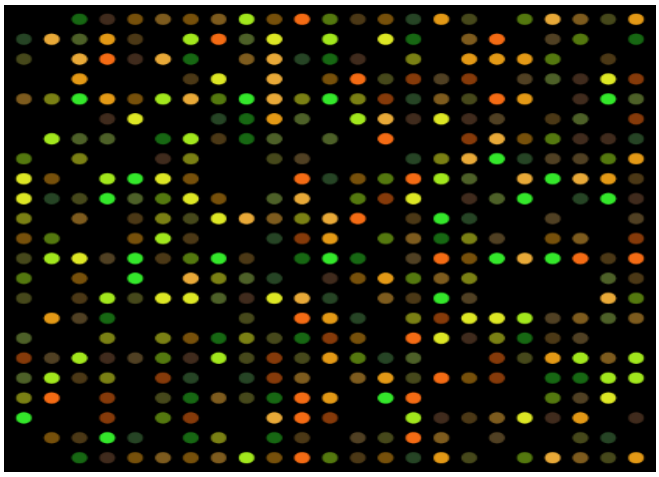

Figure 8: DNA microarray chip with dual-channel version; Taken from[118]**, © Guillaume Paumier, licensed under CC BY-SA 3.0**

6. **Gene-Based Approach:** Developed in the past 10 years, the strategy based on the resemblance of molecular actions induced from profiling of gene expression has emerged as a propitious strategy for repurposing of a drug[119]. Likewise, Connectivity Map (CMap) offers a systematic and data-driven technique for recognizing relations amongst genes, disease, and drugs. The CMap catalog contains approximately 1400 FDA-licensed molecules. Moreover, numerous CMap-rooted in-silico techniques have been developed and effectively put in to invent therapeutics for several disorders[120]–[122].

   This strategy explores the inverse connection of disease and the drug by differentiating the gene expressions of the two. The gene expressions derived from omnibus library[123] was contrasted with the gene expressions derived from the CMap. As an outcome, novel drug-disorder pairs were recognized, and one of the pair was approved in pre-clinical trials also. Main benefit of this approach is, it identifies a novel mechanism for therapeutics and mechanisms with more molecular- and genetic-level are embraced.

7. **Current approved and under trial drug candidates:** T2DM is a complex disorder possessing various mechanisms of action which contribute to abnormal control of glucose. It encompass modifications in activation of numerous stress-related pathways, lipid metabolism, and elevated tissue systemic and specific inflammation. Promiscuity of these path physiological mechanisms has precipitated re-evaluation of drugs that act as potent therapies for treating T2DM.

   Niclosamide ethanolamine (NEN), which is a mitochondrial uncoupling therapeutic. Some researchers have hypothesized that NEN will influence metabolism of energy to obstruct diabetes disease. They exhibited that an oral NEN would increase metabolism of lipid and expenditure of energy. These results retarded the outset of diabetes disease both in genetic and dietary models of T2DM. Thus it is safe and well-tolerated therapeutic and can be a new anti-diabetic drug agent[124].

Obesity and T2DM are distinguished by poor-quality inflammation. But it still remains unanswered whether the improved inflammatory condition is a consequence or a cause of insulin resistance. However, methods to decrease inflammation have been observed to improve glycaemic control and insulin sensitivity[125]. Salicylate, a therapeutic employed to cure inflammation and pain, was suggested as the feasible anti-diabetic medication[126]. Human trials showed utility on inflammation, insulin sensitivity, and glycaemic parameters[127], with few probable cardiorenal problems[128].

Also, few therapeutics focusing the inflammatory routes have been emerged in preclinical trials. For instance, amlexanox, a drug which is employed to clinically cure asthma and aphthous ulcers, possesses potential to treat T2DM rodents. Curing mice models with amlexanox significantly elevated expenditure of energy with improvement in reduction of steatosis and insulin sensitivity[129]. The mode of functioning for this compound was noticed to be active in T2DM and obesity. Diacerein, another therapeutic which hampers action of interleukin-1b, offers favourable effects on sensitivity of insulin and metabolic control and is clinically employed to cure inflammatory disorders like osteoarthritis[130]. Furthermore, anti-inflammatory agents such as hydroxychloroquine, used for nursing rheumatoid diseases and malaria, have also displayed antidiabetic effects in several clinical studies[131].

To recognize the anti-diabetic potent of matrine, some scientists used a unique strategy to target the key metabolic organ. Apart from treating hepatic tumors and hepatitis, matrine was chosen for studying obese mice as it can penetrate in the liver with some minor adverse impacts. This drug enhance tolerance of glucose, ameliorate hepatic steatosis, and reduce adiposity without acting on calorie consumption[132].

Also, various potent novel T2DM drugs have appeared from repurposing of the drugs employed to cure cholestasis and biliary cirrhosis. These encompass many bile acids and their derivatives like tauroursodeoxycholic acid[133]. The mechanism of action of these agents in enhancing the symptoms of diabetes varies but these include alterations in agonism of the farnesoid X receptor, energy expenditure, Takeda G protein-coupled receptor 5, and mitigation of endoplasmic reticulum stress. Colesevelam, a medication affecting metabolism of bile acid have been repurposed for T2DM. Originally, it was evolved to reduce circulating levels of lipid. The clinical analysis exhibited supplemental action of the drug to enhance glycaemic control and so, it is validated for T2DM use[134].

MLR-1023, another fascinating medication possessing capabilities for drug repositioning in T2DM, was recognized by its use in in-vivo phenotypic screen. It is a clinical-level drug developed to treat gastric ulcers. It showed favourable outcomes in enhancing insulin action and metabolism of glucose in animal studies[135].

III. COMPUTATIONAL APPROACHES AND TECHNIQUES FOR ANTIDIABETIC DRUG DISCOVERY

Computational drug design approaches provide advantages for mechanisms, experimental findings, and novel recommendations for the molecular arrangements for novel

synthesis. Various drugs were optimized and discovered employing in-silico techniques and have even gained the approval of U.S. Food and Drug Administration (FDA)[136],[137]. Computational drug discovery approaches could elevate the rate of hit of new anti-diabetic drugs as it uses huge chemical search space in order to detect an appropriate target in contrast to traditional combinatorial chemistry and high-throughput screening. After comparing numerous studies, it was noted that virtual screens have a strike rate of 10 to 1700-times in contrast with conventional screening[138]–[140].

1. **Computational drug repurposing strategies based on transcriptional signatures:** An indeed systematic and comprehensive technique to leverage the transcriptional signatures is the CMap project[119]. For each gene evaluated, the perturbation outline of each therapeutic in the bibliography holds a transcriptional task, which is known as gene signature. These signatures aid in differentiating the mechanism of various drugs at the transcriptional stage and are effectively put in many examples for drug repositioning. CMap was employed to recognize new anti-nociceptive and analgesic effects of phenoxybenzamine, which is an anti-hypertensive medication[141]. Also, successive studies on inflammatory rat model confirmed its analgesic actions. Contrary to, bi-clustering methods were practiced to CMap for grouping together co-regulated genes with several drugs[142].

   Signature matching focuses on differentiating the distinctive property or 'signature' of one therapeutic, clinical phenotype, or disorder, with another[143],[144]. A drug signature can be attained by 3 kinds of data: transcriptomic, metabolomics, or proteomic data; side effects and chemical structures[145]. Linking the transcriptomic signatures is utilised to formulate drug-drug comparisons[146] and drug-disease comparisons (drug-disease similarity)[147]. It is a rational technique for recognising repositioning possibilities, however non-availability of data on assessments and side effects for some therapeutics can restrict its application[148].

2. **Network-based Approaches:** These approaches aim at organizing a relationship among several biological molecules to discover novel emanated characteristics and to study the instigation of various phenotypes in distinct circumstances by cellular systems. In the pharmacological frame, a network is represented as a connected graph, where the node represents either a molecular unit, its active target, the modifier molecule, or the target route, whereas an edge depicts either an indirect or direct relation between the two linked nodes. Eventually, the toxicity and efficacy of a medication are the consequences of a complicated interaction amongst the distinct cellular elements. Network-based studies has emerged as a broadly employed technique for in-silico drug repurposing. Some scientists designed a disorder-resemblance network utilizing the gene expressions available in the public domain[149]. Also, a new strategy is developed to reposition medicines for cancer treatments by leveraging the askew impacts which can influence cancer cell signaling routes[150].

   It also assists the conformational analysis step. Conformational analysis is a method that deals with minimum energy configurations of deformable molecules through numerous calculation strategies and the network includes differentiating the receptor site of a molecule with another molecule and calculates the most energetic conformation.

3. **Ligand-based Approaches:** These approaches are rooted on a basic notion that akin compounds possibly possess akin biological characteristics. In the drug repositioning process, these approaches are widely employed to predict and analyze the actions of the ligand for novel active sites. The common libraries, such as DrugBank, PubChem, and ChEMBL, comprises of numerous bioactive molecules and information like cellular activity, binding affinity, ADMET properties[151]–[153]. Latest advancements involve those directories that focuses on failed medications, repurposed therapeutics, their remedial signs, and bioactivity[154],[155].

   Ligand- rooted strategies rely upon the chemical analysis of previously known compounds. Furthermore, a strong resemblance does not certainly promise action on the secondary target, after all the localized structural disparities in the chemical scaffolds could result in "activity cliffs"[156]. However, this shortcoming would ultimately be exterminated by huge variation in structures in the bioactivity libraries[157]. In another research, 23 novel therapeutic-target relations were predicted employing the resemblance ensemble strategy[158]. The pharmacophore screening approach is also identified as a beneficial method for drug repositioning[159]. It was shown that phenotypic and chemical similarities complement each other and combining the predictions of both these techniques will be useful[160].

4. **Ligand-based machine learning and chemogenomics in drug repurposing:** Various computational methods are put in to ligand-rooted chemo-genomic drive[161],[162]. Earlier, machine learning algorithms were accessible to aid the drug repurposing procedures[163]. And approaches which includes multi-task learning and deep learning had successfully been employed in the chemo-genomic analysis[164]. Furthermore, matrix factorization techniques provide a chance to combine bioactivity score with associated parameters, like disease information, in the single framework[165]. On the other side, additional methods which are stimulated by e-websites show fascinating outcomes in recognizing the novel therapeutic–target relation[166]. In a study, it was highlighted that algorithms perform fine while anticipating the novel therapeutic–target relations when the resemblance of the drug and the target was contemplated. Thus, machine-learning approaches perform a vital part in the computational chemo-genomics[143].

   Monte Carlo simulation is rooted on the principles of statistical mechanics which produces distinct conformations of the system by in-silico simulation in order to permit the preferred numerical, thermodynamic, and structural characteristics. Based on the classical mechanics, molecular dynamic (MD) simulation is also a potent approach that rely upon the simulation of molecular movement for every atom and also elevates the position and speed of every atom with respect to time. These approaches uses intrinsic dynamics of the system to explore the conformers with low energy and these could be utilized for the sampling of the conformational space of large systems.

5. **Structure-based approaches:** Proteins having akin structures possibly possess akin functions and to identify akin ligands, for instance dual inhibitors for the epidermal growth factor receptor (EGFR) and EGFR B2. In drug repositioning process, comparison of the protein is done to recognize the secondary targets of the already accepted therapeutics[167].

Protein sequences are used to form phylogenetic trees, which are represented by kinome[168]. Contemporary approaches to execute multi-sequence arrangements, like BLAST, are broadly utilized and accessible via web servers. A small difference localized at key positions hold the protein kinases or other mutations, which could greatly affect binding of the ligand[169]. A research on resemblance ensemble technique exhibited that akin ligands can attach with proteins having distantly associated sequences[170]. Overall, the localized binding site resemblances are more essential than universal resemblances to find out drug repurposing and poly-pharmacology[171],[172].

QSAR tools are employed to depict an association between property and structural descriptors of various molecules possessing their biological activities. These descriptors explain several characteristics of a molecule like topologic, hydrophobic, steric, and electronic properties which are calculated by experimental and in-silico approaches[173],[174]. Hologram QSAR is also a distinctive procedure, where exact 3D data about the ligands is not required. In this technique, the compound splits into the molecular fingerprints, inscribing the recurrence of numerous types of molecular fragments. The molecular holograms are created by branched and linear fragments, varying from 4-7 atoms in size[175].

IV. CONCLUSION AND FUTURE PERSPECTIVES

The growing incidence and complexity of diabetes cases across comorbidities, age, lifestyle etc. make the parallel development of new drug candidates necessary. Unlike traditional drug discovery methods, computational methods and repurposing provide cheap, fast and effective leads with a higher success rate. This becomes especially significant considering the present and growing inaccessibility to anti-diabetic drugs and the substantial economic investment in bringing a drug from bench to bedside.

Drug repurposing has proved itself as an attractive area of research enabling insights into the additional therapeutic potential of pre-existing drugs. The approach has clear advantages in terms of shortening the drug development process by using safety certified drugs. This was clearly validated by the repurposing of remdesivir, favipiravir, tocilizumab etc. in response to the COVID-19 pandemic[176],[177],[178]. These repurposed drugs provided safe emergency relief in absence of alternatives, allowing for valuable time for development of healthcare protocols and vaccine research. It also crucially informs the computational drug design and molecular modelling process for new leads and combinations.

Cutting-edge computational methods such as CoMFA, 3-D mapping, screening, gene analysis, docking and dynamics etc. inform the computational drug repurposing process. With the advent and leaps in areas such as artificial intelligence and deep learning, the approach is expected to become more robust[179]. While the experimental and clinical

validation of drug candidates remains a cornerstone of drug development, undoubtedly computational methods can support and strengthen the process manifold.

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