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A Review of Drug Design Techniques Assisted by Computers to Combat Diabetes

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Abstract

Diabetes mellitus is a global health concern characterized by chronic hyperglycemia and associated complications. The creation of innovative medicines with enhanced efficacy and safety profiles continues to be a top focus, notwithstanding improvements in treatment. A useful method in drug development, computer-aided drug design (CADD) makes it easier to identify possible therapeutic candidates and optimise lead molecules. An extensive synopsis of CADD tactics used in the fight against diabetes is given in this review. It explores virtual screening, molecular docking, pharmacophore modeling, and molecular dynamics simulations, highlighting their applications in identifying novel targets, lead compounds, and multi-target drug combinations. Additionally, it discusses challenges, such as data integration, experimental validation, and ethical considerations, along with opportunities for future research, including the integration of artificial intelligence, high-throughput screening, and personalized medicine approaches. This review underscores the potential of CADD to accelerate the discovery of innovative therapeutics for diabetes management, ultimately improving patient outcomes and addressing unmet clinical needs.

Keywords: Diabetes mellitus, computer-aided drug design (CADD), virtual screening, molecular docking, pharmacophore modelling, molecular dynamics simulations, drug discovery, therapeutic targets, personalized medicine, artificial intelligence

INTRODUCTION

Diabetes, often known as diabetes mellitus, is a long-term metabolic disease marked by high blood sugar levels brought on by insufficient insulin synthesis, insulin resistance, or both. The World Health Organisation (WHO) reports that millions of people worldwide suffer from diabetes, and that the disease's incidence has been rising over time [1]. It poses a significant burden on healthcare systems and individuals alike, leading to complications, such as cardiovascular disease, kidney failure, and blindness if not effectively managed [2]. In the face of this growing epidemic, the development of effective treatments for diabetes is paramount [1]. Traditional drug discovery methods often involve time-consuming and costly trial-and-error approaches, making the process inefficient and resource-intensive. However, with the advent of computer-aided drug design (CADD), there is renewed hope for accelerating the discovery and development of novel therapeutics for diabetes. CADD integrates computational techniques, algorithms, and molecular modeling tools to predict the interactions between potential drug candidates and their biological targets, thereby streamlining the drug discovery process [3]. Researchers can reduce the likelihood of clinical trial failure, optimise the pharmacological features of promising

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lead drugs, and identify them more quickly by utilising computer power [2]. The goal of this analysis is to give a thorough summary of all the different CADD tactics used in the fight against diabetes [4]. It will delve into the intricacies of molecular modeling, structure-based and ligand-based drug design, as well as virtual screening techniques [5]. Furthermore, it will explore potential molecular targets for drug intervention in diabetes, such as the insulin receptor, glucose transporters, and key enzymes involved in glucose metabolism [3]. By synthesizing existing knowledge and highlighting recent advancements in the field, this review seeks to underscore the pivotal role of CADD in shaping the future of diabetes treatment [4–7]. Ultimately, it is hoped that this endeavor will contribute to the development of safer, more efficacious therapies that can improve the lives of millions of individuals living with diabetes worldwide [7]. Diabetes mellitus, a long-term metabolic disease marked by high blood glucose levels, is a major global health concern [2]. Globally, the prevalence of diabetes is expected to impact 463 million persons; reasons contributing to this increase include ageing populations, bad diets, and sedentary lifestyles [1]. Numerous side effects of this epidemic, including as neuropathy, nephropathy, cardiovascular illnesses, and retinal, place a significant strain on economies and healthcare systems [3]. Despite the availability of various pharmacological interventions, including insulin therapy, oral antidiabetic agents, and lifestyle modifications, achieving optimal glycemic control and preventing long-term complications remain elusive for many patients [5]. Moreover, existing treatment modalities are associated with limitations, such as adverse effects, treatment resistance, and inadequate efficacy, underscoring the urgent need for novel therapeutic strategies [1]. Computer Aided Drug Design, A tools in designing Antidiabetic agent shown in Figure 1.

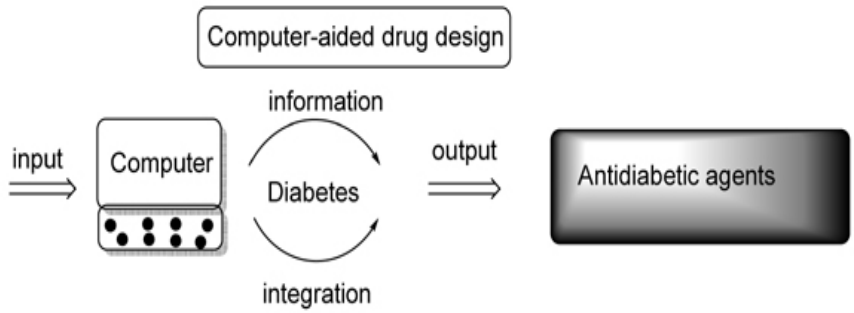

Figure 1. Computer aided drug design, a tool in designing antidiabetic agent.

UNDERSTANDING DIABETES

A class of metabolic diseases known as diabetes mellitus is typified by hyperglycemia brought on by abnormalities in either insulin action or secretion, or both [3]. The pathophysiology of diabetes is complex and involves multiple mechanisms, including impaired insulin production by pancreatic β-cells, peripheral insulin resistance, abnormal glucose metabolism, and dysfunctional hormonal regulation [1].

One of the key features of diabetes is insulin resistance, where target tissues, such as muscle, liver, and adipose tissue exhibit reduced responsiveness to insulin [2]. As a result, there is less uptake and use of glucose, which raises blood glucose levels. Additionally, β-cell dysfunction or loss contributes to inadequate insulin secretion, further exacerbating hyperglycemia [3].

Types of Diabetes

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are the two primary forms of the disease. The autoimmune death of pancreatic β-cells, which results in complete insulin insufficiency and reliance on exogenous insulin therapy, is the hallmark of type 1 diabetes [5]. Conversely, T2DM usually results from a confluence of lifestyle variables, including obesity and sedentary behaviour, and genetic susceptibility [3]. Insulin resistance and relative insulin insufficiency are its defining characteristics [3].

The goal of the diabetic treatments available today is to keep blood glucose levels within a specific range to avoid problems. These include changing one's diet and level of activity, using oral diabetes medicines (such as metformin or sulfonylureas), administering insulin subcutaneously, and utilising cutting-edge treatments like sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists (SGLT2 inhibitors) [4]. Despite the availability of these treatments, diabetes management remains challenging, and there is a continuous need for new therapeutic approaches. The elucidation of the underlying pathophysiology of diabetes has paved the way for targeted drug discovery efforts aimed at addressing specific molecular pathways implicated in the disease [6, 8].

Pathophysiology of Diabetes

A range of metabolic conditions collectively referred to as diabetes mellitus are marked by hyperglycemia, which is brought on by abnormalities in either insulin action or secretion, or both [9]. The primary autoimmune cause of type 1 diabetes mellitus (T1DM) is the death of pancreatic beta cells, which results in complete insulin insufficiency [6]. In contrast, type 2 diabetes mellitus (T2DM) typically arises from a combination of insulin resistance and impaired insulin secretion, often exacerbated by genetic predisposition, obesity, and lifestyle factors.

In T1DM, autoimmune destruction of beta cells mediated by T lymphocytes and autoantibodies results in a loss of insulin production, necessitating exogenous insulin therapy for survival. In contrast, T2DM is characterized by insulin resistance, wherein target tissues, such as muscle, liver, and adipose tissue exhibit reduced responsiveness to insulin signaling, leading to impaired glucose uptake and glycogen synthesis [10]. Compensatory hyperinsulinemia initially maintains euglycemia, but over time, pancreatic beta cells fail to sustain adequate insulin secretion, resulting in hyperglycemia.

The pathophysiology of diabetes is thought to be influenced by several key molecular pathways, including as inflammation, oxidative stress, dysregulation of glucose metabolism, and mitochondrial dysfunction. The aforementioned anomalies play a role in the emergence of diabetic complications, encompassing both macrovascular and microvascular manifestations, such as diabetic retinopathy, diabetic nephropathy, and peripheral artery disease [7].

Targeted therapy strategies require an understanding of the complex interactions between genetic, environmental, and behavioural factors that underlie the pathophysiology of diabetes. By elucidating the molecular pathways involved in disease pathogenesis, researchers can identify novel drug targets and design innovative treatment strategies aimed at restoring glucose homeostasis and preventing the progression of diabetes and its associated complications [8].

CURRENT THERAPEUTIC APPROACHES

The management of diabetes mellitus relies on a multifaceted approach that encompasses lifestyle modifications, pharmacological interventions, and, in some cases, insulin therapy. Changes in lifestyle, like as eating habits, consistent exercise, and weight control, are essential for maintaining glycemic control and lowering the risk of complications [11]. Furthermore, self-management techniques and patient education are essential parts of diabetes care since they enable patients to make better decisions and change their behaviour.

Pharmacological interventions for diabetes include a diverse array of oral antidiabetic agents and injectable therapies aimed at lowering blood glucose levels and improving insulin sensitivity [8]. Oral antidiabetic medications target various aspects of glucose metabolism to achieve glycemic control. These agents include biguanides (e.g., metformin), sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and alpha-glucosidase inhibitors [10]. In addition to oral medications, injectable therapies, such as insulin and glucagon-like peptide-1 (GLP-1) receptor agonists are used in the management of diabetes, particularly when oral agents alone are insufficient to achieve glycemic targets [12]. In contrast to GLP-1 receptor agonists, which increase satiety, inhibit glucagon secretion, and stimulate insulin secretion to improve

glycemic control and weight management, insulin treatment attempts to replicate natural insulin production and control blood glucose levels. Despite the efficacy of existing therapeutic modalities, several challenges persist in diabetes management [11]. These include the progressive nature of the disease, treatment adherence issues, hypoglycemia, weight gain, and cardiovascular and renal side effects associated with certain medications. Furthermore, the heterogeneity of diabetes phenotypes and individual responses to treatment underscore the need for personalized approaches to diabetes care [9].

Computer-aided Drug Design Techniques

Computer-aided drug design (CADD) encompasses a diverse array of computational techniques and algorithms aimed at accelerating the drug discovery process. By leveraging the power of computers and sophisticated software tools, researchers can predict the interactions between small molecules and biological targets with remarkable accuracy [10]. This section will delve into the key techniques employed in CADD for designing anti-diabetic drugs.

Molecular Modeling

Molecular modeling involves the computational representation and manipulation of molecular structures to understand their properties and behavior. Because it enables researchers to examine the three-dimensional structure of biological targets, like enzymes or receptors, and their interactions with possible drug compounds, this technology is crucial to the drug development process. Quantum mechanics computations, energy minimization, and molecular dynamics simulations are examples of molecular modelling techniques [11–15].

Structure-Based Drug Design

Structure-based drug design (SBDD) relies on the knowledge of the three-dimensional structure of a target protein to design novel therapeutics that interact with specific binding sites [16]. In the context of diabetes, SBDD enables researchers to identify small molecules that modulate key proteins involved in glucose metabolism, insulin signaling, and other relevant pathways. Techniques, such as docking studies, molecular docking, and virtual screening are commonly used in SBDD to predict the binding affinity and mode of interaction between ligands and targets.

Ligand-Based Drug Design

Ligand-based drug design (LBDD) focuses on the structural and physicochemical properties of known ligands (i.e., molecules that bind to the target) to design new compounds with improved pharmacological activity [13]. In LBDD, computational methods, such as quantitative structure-activity relationship (QSAR) analysis, pharmacophore modeling, and similarity searching are utilized to identify structurally related compounds with desired biological activity. When the target protein's three-dimensional structure is unavailable or difficult to obtain, LBDD is especially helpful [8].

Computerised Screening

In the context of diabetes drug discovery, virtual screening can be employed to prioritize compounds that have the potential to modulate specific targets or pathways implicated in the disease [13]. Methods, such as molecular docking, pharmacophore-based screening, and machine learning algorithms are commonly used in virtual screening campaigns to identify lead compounds for further experimental validation. By integrating these computational techniques into the drug discovery pipeline, researchers can expedite the identification and optimization of lead compounds for the treatment of diabetes. CADD offers a cost-effective and time-efficient approach to drug design, ultimately leading to the development of safer and more efficacious therapeutics for patients living with diabetes [2].

Despite the availability of various pharmacological interventions, including insulin therapy, oral antidiabetic agents, and lifestyle modifications, achieving optimal glycemic control and preventing long-term complications remain elusive for many patients. Moreover, existing treatment modalities are associated with limitations, such as adverse effects, treatment resistance, and inadequate efficacy, underscoring the urgent need for novel therapeutic strategies [11].

Applications of CADD in Diabetes Drug Discovery

Identification of Novel Drug Targets

CADD (computer-aided drug design) makes it easier to find possible therapeutic targets that may be connected to the aetiology of diabetes. By integrating bioinformatics, genomics, and systems biology approaches, researchers can elucidate the molecular mechanisms underlying disease pathogenesis and identify druggable targets for intervention [17]. Target identification may involve the analysis of protein-protein interactions, metabolic pathways, and gene expression profiles associated with diabetes and its complications.

Lead Identification and Optimization

CADD techniques, such as virtual screening, molecular docking, and pharmacophore modeling are employed to identify and optimize lead compounds with therapeutic potential for diabetes treatment. Virtual screening enables the rapid screening of compound libraries to prioritize molecules with predicted activity against target proteins involved in glucose metabolism, insulin signaling, and other relevant pathways [14]. Using molecular docking to guide the selection of lead compounds for additional optimisation, it is easier to investigate ligand-receptor interactions and anticipate binding affinities. Pharmacophore modeling aids in the identification of structurally diverse compounds that share common pharmacophoric features essential for biological activity, facilitating the design of novel drug candidates with improved potency and selectivity [2].

Structure-Based Drug Design

Structure-based drug design (SBDD) involves the rational design of small molecule ligands based on the three-dimensional structure of target proteins. Structure-activity relationships (SAR) are clarified, the binding interactions between ligands and target proteins are investigated, and lead compounds are optimised for better binding affinity and pharmacokinetic characteristics using SBDD techniques such molecular docking and molecular dynamics simulations [5]. SBDD approaches have been applied to target key enzymes and receptors involved in glucose metabolism, insulin secretion, and insulin sensitivity, offering opportunities for the development of novel therapeutic agents for diabetes management.

Prediction of Drug Efficacy and Safety

CADD methods can aid in the prediction of drug efficacy and safety profiles, helping to prioritize lead compounds with favorable pharmacological properties and reduced risk of adverse effects [7]. Quantitative structure-activity relationship (QSAR) modeling, machine learning algorithms, and computational toxicology approaches are utilized to predict the pharmacokinetic, pharmacodynamic, and toxicological properties of drug candidates, guiding the selection of compounds with optimal therapeutic index for further preclinical and clinical evaluation. Predictive modeling techniques can also assist in identifying off-target effects and potential drug-drug interactions, mitigating safety concerns during the drug development process [3].

Accelerated Drug Discovery and Development

CADD shortens the time and expense involved with traditional experimental procedures by expediting the lead identification and optimisation process, which in turn speeds up the drug discovery and development process [8]. Integrating computational modeling with experimental validation enables researchers to prioritize promising drug candidates for further preclinical and clinical evaluation, expediting the translation of research findings into clinical practice. CADD-driven drug discovery programs have the potential to deliver innovative therapeutic solutions for diabetes and other complex diseases, addressing unmet medical needs and improving patient outcomes [10].

Virtual Screening for Natural Products

Natural products have long been a source of inspiration for drug discovery, and virtual screening techniques offer a powerful approach to explore their potential therapeutic utility in diabetes

management. Virtual screening of natural product databases allows researchers to identify bioactive compounds with diverse chemical scaffolds and mechanisms of action that may modulate key targets implicated in glucose homeostasis, insulin sensitivity, and pancreatic beta-cell function [13]. By leveraging the chemical diversity of natural products and the predictive power of computational models, virtual screening enables the rapid identification of lead compounds with novel structures and pharmacological properties for diabetes drug discovery.

Fragment-Based Drug Design

Fragment-based drug design (FBDD) is a rational approach to drug discovery that focuses on identifying small molecular fragments capable of binding to target proteins and elaborating them into high-affinity lead compounds. FBDD methods, such as fragment screening and fragment linking, are well-suited for targeting protein-protein interactions and challenging drug targets in diabetes research. By fragmenting larger chemical libraries into smaller, more manageable subsets, FBDD enables efficient exploration of chemical space and identification of fragment hits with desired binding properties. Computational techniques play a crucial role in fragment-based drug design by facilitating fragment screening, hit optimization, and lead generation through molecular docking, pharmacophore modeling, and structure-based design approaches [15].

Multi-Target Drug Design

Diabetes is a complex multifactorial disease characterized by dysregulation of multiple physiological processes, including insulin secretion, insulin action, glucose metabolism, and inflammation. Multi-target drug design strategies aim to address this complexity by simultaneously modulating multiple targets implicated in disease pathogenesis, thereby achieving synergistic therapeutic effects and improving treatment outcomes [12]. Computational methods, such as network pharmacology, systems biology modeling, and polypharmacology analysis are employed to identify and prioritize combinations of drug targets and design multi-target ligands with optimal pharmacological properties. By leveraging the integrative power of computational modeling and data-driven approaches, multi-target drug design holds promise for overcoming the limitations of single-target therapies and developing more effective treatments for diabetes and its complications [18–22].

Personalized Medicine Approaches

To maximise therapeutic outcomes and reduce side effects, personalised medicine seeks to customise medical treatment to each patient's unique characteristics, such as genetic makeup, metabolic profile, and disease phenotype. In the context of diabetes, personalized medicine approaches utilize computational modeling and predictive analytics to stratify patients into subgroups based on genetic risk factors, metabolic biomarkers, and clinical phenotypes, enabling more precise diagnosis, prognosis, and treatment selection [8]. Machine learning algorithms, genetic association studies, and pharmacogenomics analysis are employed to identify biomarkers of drug response and develop predictive models for personalized diabetes management. By integrating patient-specific data with computational models, personalized medicine approaches have the potential to revolutionize diabetes care by optimizing treatment selection, dosage adjustment, and monitoring strategies tailored to individual patient needs [21].

TARGETS FOR DRUG DESIGN IN DIABETES

Identifying suitable molecular targets is crucial for the successful development of anti-diabetic drugs. In this section, we will explore potential targets for drug design in diabetes, including key proteins and pathways implicated in the pathogenesis of the disease.

Insulin Receptor

Because the insulin receptor mediates the effects of insulin on cells, it is essential for maintaining glucose homeostasis. Insulin binds to its receptor, initiating a series of intracellular signalling processes that result in the intake of glucose, the creation of glycogen, and the synthesis of proteins. One of the main characteristics of type 2 diabetes, insulin resistance, is the dysregulation of insulin signalling

pathways [23]. Targeting the insulin receptor and its downstream signaling components presents an attractive strategy for improving insulin sensitivity and glycemic control in diabetic patients.

Glucose Transporters

Integral membrane proteins called glucose transporters (GLUTs) help move glucose across cell membranes. GLUTs play a crucial role in regulating glucose uptake in various tissues, including skeletal muscle, adipose tissue, and the liver [16]. In diabetes, dysregulation of GLUT expression and activity contributes to impaired glucose uptake and hyperglycemia. Targeting GLUTs to enhance glucose uptake in insulin-sensitive tissues represents a promising approach for managing diabetes and improving insulin sensitivity [13].

Enzymes in Glucose Metabolism

Several enzymes involved in glucose metabolism are potential targets for drug intervention in diabetes. For example, enzymes, such as glucokinase, hexokinase, and glycogen synthase are involved in glucose phosphorylation and glycogen synthesis, respectively. Modulating the activity of these enzymes can impact glucose utilization and storage, thereby influencing blood glucose levels. Similarly, enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), represent potential targets for inhibiting hepatic glucose production in diabetes [21].

By targeting these key proteins and pathways involved in glucose homeostasis, researchers can develop novel therapeutics with the potential to improve glycemic control and prevent the progression of diabetes and its associated complications [14]. The creation of safer and more efficient diabetic treatments can result from the rational design and optimisation of drug candidates that target these molecular targets with the use of computer-aided drug design (CADD) techniques [12].

CASE STUDIES AND SUCCESS STORIES

In this section, we will explore notable case studies and success stories highlighting the application of computer-aided drug design (CADD) in the development of anti-diabetic drugs. These examples illustrate the effectiveness of CADD techniques in identifying promising drug candidates and advancing them through the drug discovery pipeline.

Development of DPP-4 Inhibitors

An oral drug class called dipeptidyl peptidase-4 (DPP-4) inhibitors is used to treat type 2 diabetes. These medications increase levels of incretin hormones including glucagon-like peptide-1 (GLP-1), which boost insulin secretion and reduce glucagon release, by blocking the function of DPP-4 [22]. The development of DPP-4 inhibitors was facilitated by structure-based drug design (SBDD) techniques, which enabled researchers to identify small molecules capable of binding to the active site of DPP-4 with high affinity and selectivity. Examples of FDA-approved DPP-4 inhibitors include sitagliptin, saxagliptin, and linagliptin [14].

Discovery of SGLT2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of anti-diabetic medications that work by preventing glucose from being reabsorbed in the renal tubules. This increases the excretion of glucose through the urine and lowers blood glucose levels [16]. The discovery of SGLT2 inhibitors was driven by virtual screening techniques, which allowed researchers to screen large chemical libraries to identify compounds with the desired pharmacological activity. Empagliflozin, dapagliflozin, and canagliflozin are examples of FDA-approved SGLT2 inhibitors that have revolutionized the treatment of type 2 diabetes [18].

Targeting PPARγ for Insulin Sensitization

Thiazolidinediones (TZDs), which are PPARγ agonists, are broadly utilised in the management of insulin resistance in individuals with type 2 diabetes. These drugs exert their effects by activating

PPARγ, a nuclear receptor that regulates genes involved in glucose and lipid metabolism [23]. The development of PPARγ agonists was supported by ligand-based drug design (LBDD) techniques, which enabled researchers to optimize the pharmacological properties of TZD derivatives for improved efficacy and safety profiles. Rosiglitazone and pioglitazone are examples of FDA-approved PPARγ agonists used in the management of type 2 diabetes [16].

CHALLENGES AND FUTURE DIRECTIONS

While computer-aided drug design (CADD) has made significant strides in advancing drug discovery efforts for diabetes, several challenges persist, and future directions warrant exploration [24]. This section addresses the challenges faced by researchers in the field of CADD for diabetes and outlines potential avenues for future research and innovation.

Data Availability and Quality

The availability and quality of data for modelling and simulation is one of the main issues in CADD. In the context of diabetes, there is a need for comprehensive datasets encompassing diverse molecular targets, ligands, and biological pathways implicated in the disease [18]. Improving access to high-quality data and databases will enhance the accuracy and reliability of computational predictions in drug design.

Target Validation and Druggability

Identifying suitable molecular targets with therapeutic potential remains a critical bottleneck in drug discovery [17]. While advances in genomics and proteomics have facilitated the identification of novel targets for diabetes, validating their druggability and clinical relevance remains challenging. Future research efforts should focus on integrating multi-omics data and employing innovative experimental techniques to validate and prioritize potential drug targets for further exploration [20].

Computational Complexity and Resources

The computational complexity of CADD methods poses practical challenges in terms of time, computational resources, and expertise required for implementation. High-performance computing resources and specialized software tools are essential for conducting molecular modeling, virtual screening, and structure-based drug design studies effectively. Addressing the computational demands of CADD while ensuring accessibility to researchers with varying levels of expertise is essential for advancing drug discovery in diabetes [21].

Translational Research and Clinical Translation

In drug discovery, bridging the preclinical research and clinical translation divide is still a major challenge. While CADD can accelerate the identification of lead compounds, translating these findings into clinically effective therapies requires rigorous preclinical validation and clinical testing. Promising medication candidates must be translated from bench to bedside with the assistance of regulatory agencies, industry, and academics working together [18].

CONCLUSIONS

To sum up, computer-aided drug design, or CADD, has shown to be an effective weapon in the fight against diabetes, providing cutting-edge methods to hasten the discovery and development of new treatments. Researchers can find potential drug candidates with improved efficacy, selectivity, and safety profiles by combining computational methods, molecular modelling, and virtual screening. Furthermore, the case studies and success stories presented in this review underscore the impact of CADD in translating computational predictions into clinically effective therapies for diabetes. From the development of DPP-4 inhibitors to the discovery of SGLT2 inhibitors and PPARγ agonists, CADD has revolutionized the landscape of diabetes treatment by providing researchers with valuable insights and tools to expedite the drug discovery process.

However, challenges, such as data availability, target validation, computational complexity, and clinical translation remain significant hurdles that must be addressed to fully harness the potential of CADD in diabetes research. Future research efforts should focus on overcoming these challenges, embracing emerging technologies, and fostering collaborative partnerships to drive innovation and advance the field of diabetes drug discovery.

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