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Molecular Docking Approaches in Diabetes

Ms. Vrushali Randive, Ms. Sakshi Gaware, Ms. Tanuja Jadhav, MS. Neha Hinge

Department of pharmaceutical Chemistry,
Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune,411014, Maharashtra, India

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ABSTRACT: Diabetes mellitus is a long-term metabolic disease characterized by high blood sugar levels caused by poor insulin production or function. Two key enzymes in carbohydrate metabolism are alpha-amylase and alpha-glycosidase [4].The changes in the body caused by type-2 diabetes include insulin resistance in the muscles, poor control of glucose production in the liver, and a decline in β-cell function. This progression ultimately results in β-cell failure [8]. The traditional way of giving insulin involves multiple daily subcutaneous injections. However, patient compliance is low because of the pain linked to this method [9]. Herbal drugs are often prescribed for this condition because they are effective, have fewer side effects based on clinical experience, and are relatively inexpensive. Herbal medicines are used to treat diseases and disorders due to their mild side effects, easy availability, and low cost. Molecular docking studies were performed to assess the affinity and interaction of chemical compounds from different plants with the enzymes. The molecular docking study confirmed the inhibitory activity of alpha-glycosidase and alpha-amylase, supporting the observed percentage of inhibitory activity [4].

KEYWORDS: Molecular Docking, Diabetes mellitus, PDB

I. INTRODUCTION

The World Health Organization released its first Global Report on Diabetes on World Health Day, April 7, 2016, highlighting the global importance of diabetes as a public health concern. Although diabetes has been recognized since ancient times and regarded as a serious illness, it was historically not a major focus for physicians or healers. In recent decades, however, the growing prevalence of diabetes has made it a significant challenge to both human health and global development [1].There is strong global political support to fight diabetes. It is part of the Sustainable Development Goals, the UN Political Declaration on NCDs, and the WHO NCD Global Action Plan. Building on these efforts can inspire joint action worldwide. Countries can take important steps to reduce the burden of diabetes. Create national committees or commissions to ensure strong political commitment, proper funding, and leadership focused on NCDs, especially diabetes, Strengthen the health ministry's role by involving different sectors, setting clear national targets, and making sure diabetes policies are well-implemented and funded,Focus on preventing obesity from early life by promoting breastfeeding, healthy eating, and physical activity, Use combined approaches such as taxes, laws, public education, and improved environments to make healthy lifestyles easier and more appealing[2].WHO aims to encourage and support effective measures for monitoring, preventing, and controlling diabetes and its complications, particularly in low- and middle-income countries. In April 2021, WHO launched the Global Diabetes Compact, a global initiative to promote lasting improvements in diabetes prevention and care, focusing on helping low- and middle-income countries. In May 2021, the World Health Assembly adopted a resolution to strengthen diabetes prevention and control. In May 2022, the World Health Assembly endorsed five global diabetes coverage targets that are set to be achieved by 2030 [3].The world report on diabetes, published by WHO, states that in many areas, poor policies for creating environments that support healthy lifestyles and limited access to quality health care lead to insufficient attention to preventing and treating the disease. This issue is particularly critical for individuals with limited resources (WHO, 2016) [20].

II. ANTIDIABETIC AGENT

The term "diabetes" comes from the Greek word "Diab," which means to pass through. This refers to the cycle of intense thirst and frequent urination. "Mellitus" is the Latin word for

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"sweetened with honey," which describes the presence of sugar in the urine [46].Diabetes mellitus (DM) is a metabolic disorder marked by high blood sugar levels. This condition happens due to problems with insulin action, issues with insulin secretion from pancreatic beta cells, or a mix of both [47].Despite having synthetic antidiabetic drugs, their side effects, limited effectiveness, and long-term complications have sparked interest in natural products as possible alternatives [48].Herbal extracts are complex mixtures of different phytochemicals. They help control blood sugar levels and reduce complications related to diabetes through various processes [50].Despite having insulin preparations and various synthetic oral antidiabetic drugs, there is a critical need to discover and develop new antidiabetic drugs. This need arises from the resistance and side effects that can occur with long-term use of existing medications [49].

2.1 Severity Domains: -Diabetes-related complications were the most frequently used areas to assess diabetes severity, as noted in 11 (61%) of the severity measures. Micro vascular complications, such as diabetic neuropathy, nephropathy, and retinopathy, as well as micro vascular events, were included. Glycaemic control was the second most commonly included area, with blood glucose and/or HbA1c levels used in eight (44%) severity measures. The complexity of antidiabetic treatment was also addressed in four (22%) severity measures; this was assessed based on insulin use and/or the number of prescribed antidiabetictherapies, including immunotherapy and drug combinations. Other areas used to evaluate diabetes severity included diabetes duration; blood pressure levels; presence of renal disease, indicated by albuminuria and/or serum creatinine; a composite score of quality of life indicators, counts of comorbidities, and prescribed medications; demographic variables such as age, gender, ethnicity, and marital status; BMI; low-density lipoprotein (LDL) levels; and a composite history of cerebrovascular and/or cardiovascular disease, severe obesity, and renal failure prior to heart transplantation[6].

2.2 Diabetes severity score: -The parameters used to create the diabetes severity score in this study included the complexity of diabetes medications, which involved using insulin or multiple oral hypoglycaemic agents (OHAs). Other factors were a longer duration of diabetes, diabetes-related kidney problems like chronic kidney disease (CKD), and the presence of cardiovascular disease (CVD). Each characteristic added one point to the diabetes severity score, allowing the total possible score to range from 0 to 5. If three or more OHAs were used, the diabetes severity score was recorded as one. If the duration of diabetes was five years or more, it also added a score of 1. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². CVD included a prior heart attack or prior stroke, identified by ICD-10 codes in one or more inpatient or outpatient records within three years before the index date. For example, a person using insulin along with CKD had a diabetes severity score of two. To assess the impact of blood glucose levels on the incidence of tuberculosis (TB), we also looked at the risk of TB based on the decile of fasting blood glucose (FBG) concentration [7].

2.3 Treatment:-Depending on the type of diabetes you have, your treatment may include blood sugar monitoring, insulin, and oral medications. Eating a healthy diet, keeping a healthy weight, and getting regular physical activity are also important for managing diabetes [8]. Two treatment strategies are important for maintaining the therapeutic effects of GLP-1. These are GLP-1R activators, also known as incretin mimetic, and incretin effect amplifiers, which are DPP-4 inhibitors [21]. Alternative medicine includes all treatments outside mainstream medicine, like herbal remedies, acupuncture, special diets, and hypnosis. It is broad and diverse [23]. The disturbance in glucose metabolism in type 3c diabetes mellitus can vary. It ranges from mild impairment to a severe form that includes frequent episodes of hypoglycaemia. This severe type is often called brittle diabetes [24].

STEM CELLS IN DIABETES: - Stem cell therapy is a promising treatment option for advanced diabetes mellitus (DM) [25]. Embryonic stem cells (ESC) can be changed into insulin-producing cells by adjusting culture conditions. In vitro differentiation of mouse ESC can create embryoid bodies. After selecting for nestin-expressing ESC, these bodies were prompted to develop into a cell-like type [26].

Nanotechnology in diabetes: -Nanotechnology in diabetes research has led to new ways of measuring glucose and delivering insulin. These methods have the potential to greatly improve the quality of life for people with diabetes [27]. These systems automatically release insulin based on changes in blood glucose levels. By linking glucose measurements with insulin delivery without

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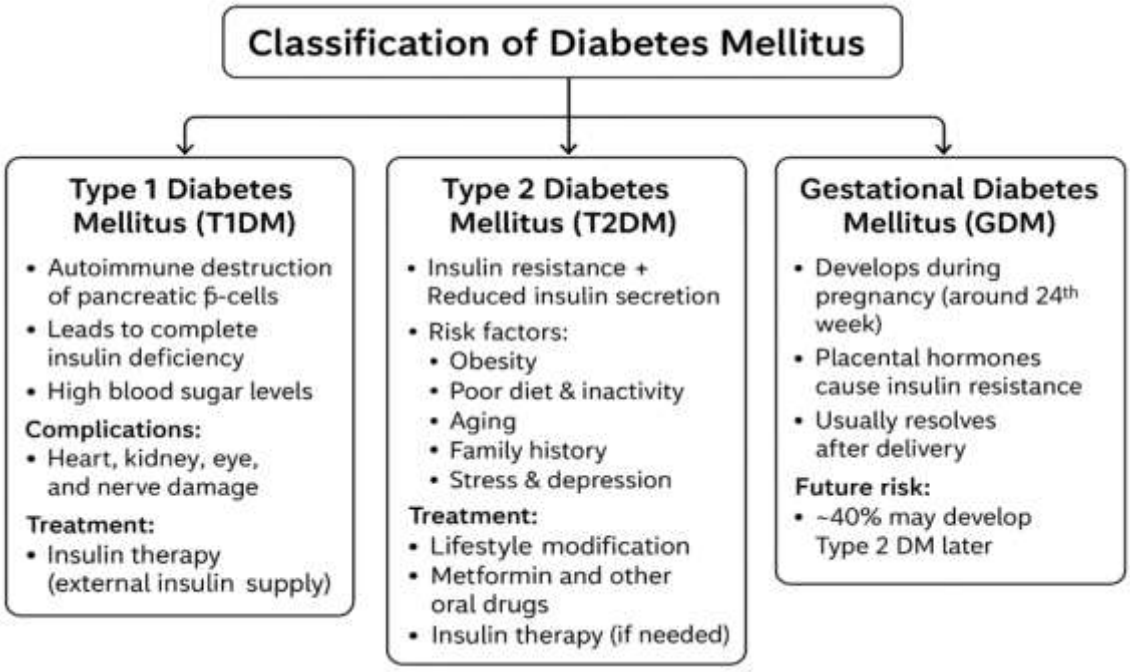
needing patient input, we can significantly enhance the health and well-being of diabetics [9].

Insulin Therapy: - Managing a patient with Type 1 diabetes focuses on reducing the chance of long-term complications, minimizing episodes of high and low blood sugar, and supporting normal growth [10]. Patients with Type 1 Diabetes Mellitus (T1DM) generally begin treatment with multiple daily insulin injections. This includes rapid-acting insulin before meals and intermediate or long-acting insulin once or twice a day. In some cases, 2 to 3 premixed insulin injections are used each day [28]. Conventional insulin therapy has limitations because regular human insulin absorbs slowly from subcutaneous tissue. Its action begins after 30 minutes to 60 minutes and peaks about 2 to 3 hours after injection [29].

2.4 Pathophysiology of Diabetes: -Regarding the pathophysiology of the disease, a problem with the feedback loops between insulin action and insulin secretion leads to abnormally high blood glucose levels. In cases of β-cell dysfunction, insulin secretion decreases. This limits the body's ability to keep glucose levels normal [11].Type 2 Insulin resistance, decreased insulin production, and eventually failure of the pancreatic beta cells causes diabetes mellitus. This leads to reduced glucose transport into the liver, muscles, and fat cells. [10]. Diabetes pathophysiology mainly rests on insulin resistance, and a number of research investigations have explored the role of factors such as environmental and genetic factors that promote type 2 diabetes mellitus [12]. There is a direct link between hyperglycaemia and both physiological and behavioural responses. Whenever hyperglycaemia occurs, the brain recognizes it and sends a message through nerve impulses to the pancreas and other organs to reduce its effect [30].

2.5 Mechanism of Action: - The cause of type 1 diabetes can be traced back to damage to the pancreatic cells from environmental or infectious agents. In people who have certain genetic traits, the immune system activates and mounts a response against the altered β-cells or against molecules in those cells that resemble viral proteins [31]. Multiple mechanisms can increase the risk of fractures in people with diabetes mellitus. Non-enzymatic glycosylation of collagen, lower bone turnover, a pro-inflammatory state, and micro vascular disease lead to both micro and macro bone structure changes. These changes reduce the bones' ability to withstand mechanical stress [32].

2.6 Types of Diabetes: -



Gestational diabetes:-Occurs when some women develop insulin resistance during pregnancy, usually around the 24th week. Hormones from the placenta likely interfere with insulin's

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effectiveness, leading to this condition. Although gestational diabetes typically resolves after childbirth, about 40% of women who experience it have a higher risk of developing type 2 diabetes later in life [12].

2.7 Curative measures for Diabetes: - Diabetes may not be fully curable, but it can be managed effectively. Proper care helps prevent or control complications. Early treatment and lifestyle changes improve a patient's quality of life [33]. Curative measures include: Stem Cell Therapy, Immune Therapy (in Type 1), GeneTherapy [34].

III. METHODS

Molecular docking has sped up drug discovery by showing how ligands interact with receptor proteins based on their structure [51].

3.1 Preparation of protein: - The PDB protein-ligand structures were processed using the Protein Preparation Wizard in the Schrödinger suite [35]. Hydrogen atoms were added after removing the original ones. Then, the bond orders for amino acid residues and the ligand were adjusted. The protonation and tautomeric states of Asp, Glu, Arg, Lys, and His were set to match a pH of 7.4. Possible orientations of Asn and Gln residues were created. Water molecules in the active site that were more than 5.0 Å from the ligand were removed. Hydrogen bond sampling and adjustments of the orientations of active site water molecules were done using PROPKA [36]. At pH 7.4. Water molecules with fewer than two hydrogen bonds to non-water molecules were removed. Next, the protein-ligand complex underwent geometry refinement using an OPLS2005 force field, with restrained minimization to achieve convergence of heavy atoms to an RMSD of 0.3 Å [37].

3.2 Preparation of Ligand: - Ligands were prepared using Ligprep from the Schrödinger suite. We obtained the initial ligand databases as collections of SMILES (simplified molecular-input line-entry system) strings that do not include 3D coordinates. The final ligand databases were in the mol2 format, which contains 3D structures. We included all structures without any pre-docking filtering. For each 2D structure in the initial databases, we generated a single low-energy 3D conformer with acceptable bond lengths and angles. After generating the 3D structures for the initial and final databases, we prepared the ligand structures for molecular docking. Ligprep used the OPLS2005 force field and charges in all ligand preparation steps. We used Ionizer at a pH of 7.4 to list all possible promoters (protonation states) and ionization states for each ligand. We generated stereoisomers for the five structures with unassigned stereo geniccentres, considering up to 32 stereoisomers per ligand. We also generated tautomeric states for chemical groups with possible prototrophictautomer's. Only the lowest energy conformer was retained for each ligand [38].

3.3 Grid Generation: - The receptor grid generation tool in Maestro calculates the grids needed for docking ligands to protein receptors. A receptor grid-generating file is used to bind ligands to the binding site. The receptor grid generation tool has several options, including receptors, site, constraints, rotatable groups, and excluded volumes. If the structure in the workspace includes a receptor and a ligand, you must identify the ligand molecule to exclude it from grid generation. This step is especially important when using the Maestro program, part of the Schrödinger suite for computational chemistry and molecular modelling. Grid formation is a key stage in this process [4].

3.4 Molecular Docking: -Molecular docking is a method for drug design that focuses on the structure. It simulates the interaction between molecules and predicts how they bind together and how strong that bond is, specifically between receptors and ligands [39]. The goal of ligand-protein docking is to predict the main binding mode(s) of a ligand with a protein that has a known three-dimensional structure [40]. The main goal of molecular docking is to find an optimized docked structure for both interacting molecules. This helps to lower the free energy of the system. The final predicted binding free energy (ΔGbind) is calculated based on factors like dispersion and repulsion (ΔGvdw), hydrogen bonds (ΔGhbond), desolvation (ΔGdesolv), electrostatics (ΔGelec), torsional free energy (ΔGtor), total internal energy (ΔGtotal), and the energy of the unbound system (ΔGunb). A thorough understanding of the basic principles that influence predicted binding free energy (ΔGbind) gives additional insight into the nature of interactions [41]. Approaches of Molecular Docking: For molecular docking, there are mainly two types of approaches. One approach uses computer simulations, where energy profiling is estimated for the ligand target [42]. TYPES OF DOCKING: Multiple mechanisms can increase the risk of fractures in people with diabetes mellitus.

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Non-enzymatic glycosylation of collagen, lower bone turnover, a pro-inflammatory state, and micro vascular disease lead to both micro and macro bone structure changes. These changes reduce the bones' ability to withstand mechanical stress. Flexible ligand docking: treats the target as a rigid molecule. This method is the most commonly used in docking. Rigid body docking: keeps both the target and ligand molecules rigid. Flexible docking: involves both interacting molecules being flexible [43,44,45].

DOCKING TOOLS

Molecular docking methodology explores the behaviour of small molecules in the binding site of a target protein. Molecular docking involves several software applications, including Discovery Studio, Auto Dock, Auto Dock Vina, and Molecular Operating Environment Schrödinger Glide. Before laboratory testing, these techniques help researchers identify potential drug candidates by analysing the strength and stability of drug-target interactions. Molecular docking has sped up drug discovery by showing how ligands interact with receptor proteins based on their structure. Docking models predict the best-docked conformer based on the overall energy of the system [5].

Docking Tools	Algorithms	Benefits	Drawbacks
Schrodinger's Glide	Docking	Predicts ligand binding modes and relative binding energies, which is useful in drug discovery.	Limited accuracy in predicting true binding affinities.Performance depends on the quality of input structures. Sometimes fails with flexible ligands or receptors.
Glide	Hierarchical method	Its ability to efficiently explore ligand-binding conformations based on geometric complementarity, offering a balance between speed and accuracy in molecular docking.	Its limited ability to account for dynamic flexibility in ligands and receptors, potentially leading to inaccuracies in predicting binding modes in highly flexible systems.
OE Docking v 3.0.0	Non-Stochastic method	Efficiently explore conformational space, ensuring comprehensive coverage and enhancing the likelihood of identifying precise ligand binding poses.	It may struggle to efficiently sample highly flexible ligands or receptor conformations, potentially leading to missed binding modes or inaccurate predictions in systems with significant conformational variability.
Flex X	LUDI	The fragment-based approach provides unbiased fragments to the active site of the receptor and utilizes the protein-ligand complex hydrogen bond.	It is difficult to find a template docked with pieces.
Mol Dock, Auto Dock, Lead finder	EP (Evolutionary programming)	Utilizing a heuristic search strategy, differential evolution is employed to anticipate cavities.	Only for flexible docking

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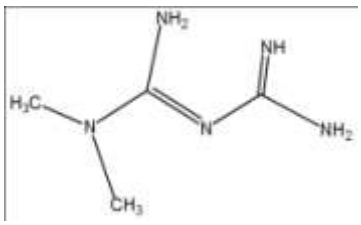
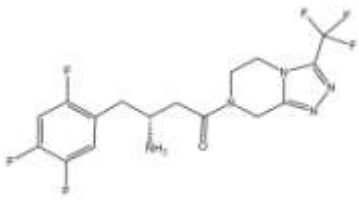
IV. PDB CODES

PDB	ORGANISM	CLASSIFICATION	MUTATION	COCRYSTAL
1B2Y	HOMOSAPIENS	HYDROLASE	NO	CALCIUM ION
1HNY	HOMOSAPIENS	HYDROLASE (U-GLYOCOSYL)	NO	
1NU8	HOMOSAPINS;SYNTHETIC	HYDROLASE	NO	2-ACETAMIDO-2 DEOXY-BRTA-GLUCOPYRONASE
2IO3	HOMOSAPIENS	HYDROLASE	NO	2-(4[(2S,5R) -2-(AMINOMETHYL) -5 ETHYLENEPYROLYINDIN -1 YL] -2-OXOETHYL AMIO] AMINO) -4 METHYL PIPERIDINE -1 YL],SONICOTINIC ACID
PDB	ORGANISM	CLASSIFICATION	MUTATION	COCRYSTAL

V. STRUCTURES

NO	Structure	Activity
1	Metformin Formula:C4H11N5 	Metformin is the most common drug in this class. It works by decreasing glucose production by the liver and increasing insulin sensitivity in tissues. Structure from: https://c-api.kingdraw.com/ClientService/WebContent/Share?id=340984&Ver=1&lang=en-us&platform=3&extToken=2vXtUHqkSLD8oSeVoZ5MoywbQNYYxGwU6mzyCYRdhKASE6EhgLzg4YeMNALTN2quictuxpZD7ZWfARktm5oLKz/qYfKSsjNHMjqNnPo2TQCVv5cTJfnz/asyEEOFSJF5ZrrpBhsAXp1XiHpTHCZeVX7GDzQTej9yBGy3uRukSq3hoNSyZfscjvJW4AMNV18K
2	Sit gliptin Formula: -C16H5F6N5O 	Sit gliptin primarily helps control high blood sugar in adults with type 2 diabetes. It is most effective when used along with a healthy diet and regular exercise. Structure from: https://c-api.kingdraw.com/ClientService/WebContent/Share?id=340982&Ver=1&lang=en-us&platform=3&extToken=ffGaO27BgN29icI340rtNGvNLX5Unn5QCYvz/Q1fqGiwEvWfwgtdF10mkmSBiUxbictuxpZD7ZWfARktm5oLKz/qYfKSsjNHMjqNnPo2TQCVv5cTJfnz/asyEEOFSJF5ZrrpBhsAXp1XiHpTHCZeVUKeDs8BximU1PclSfcMaZXhoNSyZfscjvJW4AMNV18K

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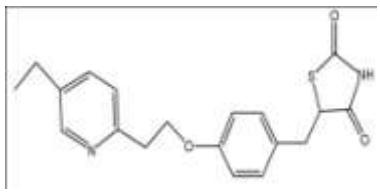
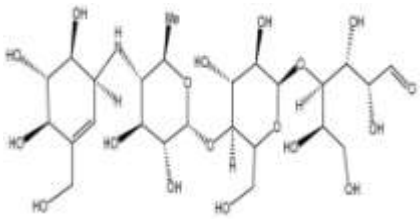
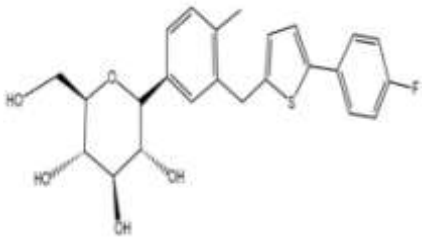
3	Pioglitazone Formula: -C19H20N2O3S 	They improve insulin sensitivity in muscle and fat tissue. Structure from: https://c-api.kingdraw.com/ClientService/WebContent/Share?id=340988&Ver=1&lang=en-us&platform=3&extToken=0TLtzZ2A5oDYLTeO+J0u8wQc3rby0+e18dkXCiBMITdwz6rQkZxrBMtv/+g4dOboictuxpZD7ZWfARktm5oLKz/qYfKSsjNHMjqNnPo2TQCVv5cTJfnz/asyEEOFSJF5ZrrpBhsAXp1XiHpTHCZeVWggqggtn+QHWOacvKnaWlnhoNSyZfscjvJW4AMNV18K
4	Acarbose Formula: - $C_{25}H_{43}NO_{18}$ 	Acarbose is an anti-diabetic drug used to treat diabetes mellitus type 2 and, in some countries, prediabetes. It is a generic sold in Europe and China as Glucobay, in North America as Precose, and in Canada as Prandase. Acarbose is a starch blocker. Structure from: https://c-api.kingdraw.com/ClientService/WebContent/Share?id=340961&Ver=1&lang=en-us&platform=3&extToken=oeKhTclbFXR+v9YYpffHY60cbUVTtS6OHCYsfW7vmBSOzqnu9dMnZ5MoYjwudm1aictuxpZD7ZWfARktm5oLKz/qYfKSsjNHMjqNnPo2TQCVv5cTJfnz/asyEEOFSJF5ZrrpBhsAXp1XiHpTHCZeVcpjSKiZxvGMsZaSzIHIwXXhoNSyZfscjvJW4AMNV18K
5	Canagliflozin Formula: - $C_{24}H_{25}FO_5S$ 	Canagliflozin, sold under the brand name Invokana among others, is a medication used to treat type 2 diabetes. It is used together with exercise and diet. It is not recommended in type 1 diabetes. It is taken by mouth. Structure from: https://c-api.kingdraw.com/ClientService/WebContent/Share?id=340970&Ver=1&lang=en-us&platform=3&extToken=R+/4uvkD0ro8ObGcxgN2QsJKRt1YuL995jPoLnSm61fk8/knTk0kk776xMq5KRSPictuxpZD7ZWfARktm5oLKz/qYfKSsjNHMjqNnPo2TQCVv5cTJfnz/asyEEOFSJF5ZrrpBhsAXp1XiHpTHCZeVR32VUaJH6LpNs4SYGsy6ufhoNSyZfscjvJW4AMNV18K

VI. CONCLUSION

Diabetes is a serious global health issue that is growing quickly among all age groups. The World Health Organization is taking many steps to prevent and control diabetes through awareness, diagnosis, and treatment programs. Managing diet, getting regular exercise, and taking medication can help control blood sugar levels. Different diabetes medications, like metformin, sit gliptin, and insulin, are used based on the type of diabetes. Recent research such as stem cell therapy, gene therapy, and nanotechnology offers new hope for improved

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treatments in the future. Molecular docking studies help discover new and effective drugs more quickly and at a lower cost. Maintaining a healthy lifestyle can prevent or delay the onset of diabetes. Early diagnosis and regular monitoring are important to avoid complications like heart and kidney problems. Governments and healthcare organizations should work together to ensure medicines and insulin are easily available to everyone. With ongoing research and public awareness, we can reduce the global impact of diabetes and help patients live healthier lives.

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