JPBIO (Jurnal Pendidikan Biologi)
Vol. 10, No. 2, November 2025, 230 – 249 //e-ISSN 2540-802X
http://jurnal.stkippersada.ac.id/jurnal/index.php/JBIO/index

# Advances in diabetes intervention: Targeting hormonal regulation, hIAPP, glucose transport, and key enzymatic pathways

Mulia Safrida Sari [1*], Lilla Puji Lestari[2], Meri M. Imun[3], Cut Sriyanti[4], Nurlaili Ramli[5]

[1] Biologi Study Program, Faculty of Science and Technology, Universitas Samudra, Indonesia
[2] Mechanical Engineering Programme, Faculty of Engineering, Universitas Maarif Hasyim Latif, Indonesia
[3] Health Analyst Diploma Programme, Faculty of Health Sciences, Universitas Bakti Tunas Husada, Indonesia
[4] Applied Midwifery Undergraduate Programme, Midwifery Department, Poltekkes Kemenkes Aceh, Indonesia
[5] Applied Midwifery Undergraduate Programme, Midwifery Department, Poltekkes Kemenkes Aceh, Indonesia

[*] Corresponding author: muliasari03@unsam.ac.id

Article Info

Article History:
Received 06 June 2025
Revised 03 September 2025
Accepted 11 November 2025
Published 30 November 2025

Keywords:
Diabetes
Insulin sensitivity
Diabetic molecular targets
Hormonal regulation
RNA binding protein

ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion or action. This condition remains a leading cause of global morbidity and mortality and is closely associated with various metabolic complications and cancer risk. This study aimed to identify potential molecular targets and hormonal regulatory mechanisms involved in diabetes management. A systematic review was conducted by searching indexed scientific articles in databases such as ScienceDirect and Google Scholar using the keywords "diabetes," "molecular targets," "insulin sensitivity," and "hormonal regulation." The analysis identified six major molecular mechanisms contributing to improved insulin action and glucose homeostasis, involving targets such as human islet amyloid polypeptide (hIAPP), α-glucosidase, dipeptidyl peptidase-4 (DPP-4), sodium-glucose co-transporter-2 (SGLT2), glucose transporter type 4 (GLUT4) translocation, RNA-binding proteins (RBPs), and key enzymatic pathways associated with glucose metabolism. The development of therapeutic approaches directed toward these pathways could significantly enhance diabetes control, improve insulin sensitivity, and prevent long-term complications.



Citation: Sari, M.S., Lestari, L.P., Imun, M.M., Sriyanti, C., & Ramli, N. (2025). Advances in diabetes intervention: targeting hormonal regulation, hIAPP, glucose transport, and key enzymatic pathways. *JPBIO (Jurnal Pendidikan Biologi), 10*(2), 230-249. DOI: https://doi.org/10.31932/jpbio.v10i2.4850

## INTRODUCTION

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin action, or both (Ozougwu et al., 2013; Shroff, 2015a). Symptoms of hyperglycemia include polyuria, polydipsia, polyphagia, myopic vision, and weight loss (Shroff, 2015a). In 2000, approximately 5.7 million Indonesians were estimated to have diabetes, a number that increased to 8.5 million by 2013 (International Diabetes Federation, 2000, 2013). The latest report from the International Diabetes Federation (2015) indicated that the number of Indonesians with diabetes aged 20-79 had risen to 10 million, with 53% of these individuals unaware of their condition. By 2040, the number is projected to reach 16.2 million, reflecting a significant rise in diabetes prevalence and its associated mortality (International Diabetes Federation, 2019).

Complications associated with diabetes include neuropathy, erectile dysfunction, nephropathy, retinopathy, and macroangiopathy, such as cardiovascular disease, stroke, and diabetic foot (Djrolo et al., 2014; King et al., 2016; Mansour et al., 2014; Ramesh et al., 2015). Additionally, diabetes has been linked to increased mortality from several cancers, including breast, colorectal, and prostate cancers (Spangler & Kirk, 2014).

Given the high prevalence and complications related to diabetes, there is an urgent need to identify innovative therapeutic strategies beyond conventional pharmacological approaches such as metformin, sulfonylureas, and insulin secretagogues. Recent research has highlighted the importance of exploring four core and two emerging aspects of diabetes intervention: (1) hormonal regulation, which modulates insulin secretion and sensitivity and plays a crucial role in glucose homeostasis (Nguyen & Le, 2012; Sharma et al., 2021); (2) human islet amyloid polypeptide (hIAPP), whose aggregation induces pancreatic β-cell apoptosis and dysfunction under hyperglycemic conditions (Roham et al., 2022); (3) incretin modulation, which enhances insulin secretion and maintains glucose homeostasis (Borah et al., 2022); (4) glucose transport mechanisms, particularly through GLUT4 translocation that facilitates glucose uptake in muscle and adipose tissues (Lee et al., 2012; Yang, 2010); (5) RNA-binding proteins (RBPs) as post-transcriptional regulators that contribute to the development of associated disease complications (Chen et al., 2022); and (6) key enzymatic pathways such as AMPK, fructose-1,6-bisphosphatase (FBPase), and protein tyrosine phosphatase 1B (PTP1B), which regulate insulin signaling, energy metabolism, and lipid-glucose balance (Sharma et al., 2021).

Understanding and targeting these molecular mechanisms provides a comprehensive foundation for developing effective strategies to improve insulin action, maintain glucose balance, and prevent long-term diabetic complications. However, an integrative understanding of these mechanisms remains limited; thus, this review aims to provide a comprehensive synthesis of their therapeutic potential.

## RESEARCH METHODS

### Research Design

This study employed a systematic review design aimed at identifying and analyzing potential molecular targets and hormonal regulatory mechanisms involved in diabetes intervention. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and scientific rigor.

### Population and Samples

The population of this study comprised 54 scientific articles consists of 51 journal articles, and 3 proceeding articles related to diabetes molecular mechanisms and therapeutic targets published in reputable journals indexed in Scopus between 2002 and 2022 such as *Bioorganic*

*Chemistry Journal* (1 article), *Phytomedicine Plus* (1 article), *Molecular Metabolism* (2 article), *Molecular Cell* (1 article), *Diabetes Research and Clinical Practice* (1 article), *European Journal of Medicinal Chemistry* (2 article), *Journal of Pharmaceutical Analysis* (1 article), *Kidney International* (1 article), *Obesity Medicine* (1 article), *Journal of Lipid Research* (1 article), *Nature Reviews Molecular Cell Biology* (1 article), *Nature Medicine* (1 article), *Frontiers in Endocrinology* (1 article), *The Journal of Clinical Endocrinology & Metabolism* (1 article), *Journal of Diabetes Mellitus* (11 article), *PLoS One* (1 article), *Kidney and Blood Pressure Research* (1 article), *Cellular Physiology and Biochemistry* (1 article), *Biomedicines* (1 article), *International Journal of Molecular Sciences* (1 article), *Journal of Community Hospital Internal Medicine Perspectives* (1 article), *The Korean Journal of Internal Medicine* (1 article), *Diabetes* (2 article), *Journal of Medicinal Chemistry* (2 article), *Diabetes & Metabolism Journal* (1 article), *Journal of Biological Chemistry* (1 article), *Cancer Cell International* (1 article), *Cardiovascular Diabetology* (1 article), *Open Heart* (1 article), *Diabetes, Obesity and Metabolism* (2 article), *Journal of Cellular and Molecular Medicine* (1 article), *Journal of Physiology and Pathophysiology* (1 article), *Endocrinology* (1 article), *Annual Review of Medicine* (1 article), *International Journal of Biological Sciences* (1 article), and *Current Topics in Medicinal Chemistry* (1 article); meanwhile published in proceedings such as *Proceedings of the National Academy of Sciences* (1 article), *Advances in Natural Sciences: Nanoscience and Nanotechnology* (1 article), and *PNAS* (*Proceedings of the National Academy of Sciences*) (1 article). The sampling technique applied was purposive sampling, where articles were selected based on their relevance to diabetes intervention strategies focusing on hormonal regulation, hIAPP, glucose transport, and key enzymatic pathways.

## Instruments

The main instrument used in this systematic review was a literature extraction matrix, which was developed to organize and *evaluate* data from the selected studies. The matrix included information such as publication year, study design, molecular targets identified, research outcomes, and conclusions relevant to diabetes therapy.

## Procedures

Data collection was *carried* out through a structured search using the keywords "diabetes," "molecular targets," "insulin sensitivity," "hormonal regulation," and "glucose transport" in the databases Google Scholar and ScienceDirect (Elsevier). Duplicate articles were removed, and the remaining studies were screened based on inclusion and exclusion criteria. Inclusion criteria included peer-reviewed articles written in English, focused on diabetes pathophysiology, therapeutic targets, or molecular mechanisms. Studies lacking sufficient methodological details or unrelated to diabetes interventions were excluded. The selected literature was then analyzed qualitatively to identify consistent molecular patterns and therapeutic mechanisms.

## Data Analysis

Data were analyzed using qualitative content analysis, which involved summarizing, classifying, and synthesizing findings from the selected literature. Each study was critically reviewed to identify key molecular pathways and intervention targets. The analysis emphasized major therapeutic directions such as hormonal regulation, hIAPP aggregation, GLUT4-mediated glucose transport, and enzymatic pathways including AMPK, FBPase, and PTP1B. Findings were synthesized and presented thematically to highlight recurrent molecular pathways and therapeutic strategies.

## RESULTS

A total of 54 relevant scientific publications were identified and reviewed to determine potential molecular targets and regulatory mechanisms involved in diabetes intervention. In general, the main classes of oral antidiabetic drugs include biguanides, sulfonylureas, meglitinides, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and α-glucosidase inhibitors (Chaudhury et al., 2017). Treatment with oral diabetes medications aims to reduce insulin resistance, decrease glucose production via hepatic gluconeogenesis, enhance endogenous insulin secretion, and limit glucose reabsorption in the body (Kerru et al., 2018).

### 1) Biguanides

Metformin, a first-line treatment for type 2 diabetes mellitus (T2DM) across all age groups, belongs to the biguanide class. It activates adenosine monophosphate (AMP)-activated protein kinase in the liver, enhances glucose uptake by inducing peripheral tissue sensitivity to insulin, and inhibits hepatic gluconeogenesis through complex effects on mitochondrial enzymes. Additionally, metformin improves insulin sensitivity by upregulating insulin receptor expression and increasing tyrosine kinase activity (Chaudhury et al., 2017).

### 2) Incretin Mimetics

Incretins are hormones that reduce gastric emptying and promote weight loss. The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), released by intestinal endocrine cells in response to food intake, play a crucial role in glucose homeostasis and glycemic control. Two classes of drugs target the incretin system: GLP-1 receptor agonists and DPP-4 inhibitors. GLP-1 receptor agonists, such as exenatide and liraglutide, resist enzymatic degradation by DPP-4, resulting in prolonged plasma presence and better glycemic control. However, they may cause renal failure. DPP-4 inhibitors, including sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin, can be used alone or in combination with metformin, sulfonylureas, or TZDs. These inhibitors lower blood glucose with minimal effects on caloric intake, thus reducing catabolic effects on muscle and total body protein mass (Chaudhury et al., 2017).

### 3) SGLT2 Inhibitors

Sodium-glucose cotransporter (SGLT2) inhibitors, a novel class of glucosuric agents, include canagliflozin, dapagliflozin, and empagliflozin. SGLT2 inhibitors lower blood glucose independently of insulin by blocking glucose reabsorption in the proximal tubules of the kidney. These drugs also promote weight loss and reduce blood pressure due to their glucose-independent mechanism of action (Chaudhury et al., 2017).

### 4) Sulfonylureas

Sulfonylureas lower blood glucose by stimulating insulin secretion from pancreatic β-cells through KATP channel blockade. They also limit hepatic gluconeogenesis and reduce lipid breakdown into fatty acids. This class includes first-generation drugs (chlorpropamide, tolazamide, and tolbutamide) and second-generation drugs (glipizide, glimepiride, and glibenclamide). Sulfonylureas are typically prescribed as second-line or adjunctive treatments for T2DM management (Chaudhury et al., 2017).

### 5) Meglitinides

Meglitinides, such as repaglinide and nateglinide, are non-sulfonylurea drugs that bind to sulfonylurea receptors on pancreatic β-cells. Their binding is weaker than sulfonylureas, categorizing them as short-term insulin secretagogues, which allows for flexible dosing. However, meglitinides require higher blood glucose levels to stimulate insulin secretion, making them less effective than sulfonylureas (Chaudhury et al., 2017).

### 6) Thiazolidinediones (TZD)

TZDs, including rosiglitazone and pioglitazone, improve insulin action by activating Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), a nuclear receptor that enhances glucose uptake in adipose, muscle, and liver tissues. PPAR-γ activation increases GLUT4 expression and translocation, reduces hepatic gluconeogenesis, and promotes lipid storage and glucose uptake in muscle. This receptor also decreases free fatty acid accumulation, lowers inflammatory cytokines, increases adiponectin levels, and maintains β-cell function. Despite these benefits, TZDs are contraindicated in patients with heart failure and are not recommended as first-line or follow-up therapy (Chaudhury et al., 2017).

### 7) α-Glucosidase Inhibitors

α-Glucosidase inhibitors target glycoside hydrolase enzymes that release glucose by cleaving glycosidic bonds. These inhibitors reduce the digestion of dietary carbohydrates, thereby lowering postprandial hyperglycemia and maintaining normal blood glucose levels. They are effective in managing diabetes by inhibiting α-glucosidase activity in the small intestine (Kerru et al., 2018).

Therapeutic targets of these oral antidiabetic drugs include human islet amyloid polypeptide (hIAPP) to improve pancreatic β-cell function, inhibition of α-glucosidase, DPP-4, and SGLT2, GLUT4 translocation to enhance glucose uptake, and RNA-binding proteins as mediators of post-transcriptional mechanisms related to diabetic complications.

The systematic review yielded six main categories of molecular targets relevant to diabetes intervention. Specifically, the synthesized data revealed that diabetes management can be directed through four primary molecular approaches and two emerging aspects, encompassing hormonal regulation, human islet amyloid polypeptide (hIAPP) aggregation, incretin modulation, glucose transport mechanisms, RNA-binding proteins (RBPs), and key enzymatic pathways related to glucose metabolism. Collectively, these molecular targets form a comprehensive network governing insulin function, glucose transport, and metabolic homeostasis in diabetes. The molecular targets involved in the pathophysiology of diabetic complications are discussed in the following sections (Discussion).

## DISCUSSION

Several treatment strategies have been implemented to manage diabetes and reduce the risk of its complications. These include the use of oral antidiabetic drugs such as metformin (Lee et al., 2012; Luo et al., 2016; Sumitani et al., 2014), glibenclamide, and insulin secretagogues, which trigger insulin secretion (IS), such as sulfonylureas or glinides (Gautier et al., 2016). Additionally, dipeptidyl peptidase-4 (DPP-4) inhibitors (Gautier et al., 2016; Kobayashi et al., 2014), chloroquine (Zhou et al., 2016), and resveratrol (Penumathsa et al., 2008) have been used to enhance insulin sensitivity, repair pancreatic β-cells, increase insulin secretion, and promote glucose transporter type 4 (GLUT4) translocation, thereby mitigating hyperglycemia.

Further investigations have explored the effectiveness of carbon dioxide therapy for diabetic foot ulcers, which helps liberate nitric oxide, improve oxygen circulation, and enhance blood flow, thus accelerating wound healing (Shalan et al., 2015). Other advanced treatments include the use of exogenous insulin pumps (Gjessing et al., 2014), pancreas transplantation, and recent advancements in genetic engineering to create new β-cells capable of increasing insulin secretion (Handorf et al., 2015). Moreover, human embryonic stem cells (hESC) are being studied as potential therapeutic agents for the treatment of diabetes (Shroff, 2015b).

### I) Hormonal Regulation Aids Glucose Metabolism

Diabetes mellitus is a metabolic disorder characterized by abnormal carbohydrate, lipid, and protein metabolism due to insulin resistance (decreased insulin sensitivity), insulin deficiency (decreased insulin secretion), or both. Insulin deficiency can result from dysfunction or functional

impairment of pancreatic β-cells, leading to elevated blood glucose levels. Insulin resistance contributes to increased glucose production in hepatocytes, while glucose absorption in muscle, liver, and adipose tissue is decreased. The combination of pancreatic β-cell dysfunction and insulin resistance exacerbates hyperglycemia and promotes the development of type 2 diabetes mellitus. The pathology of diabetes mellitus develops when the feedback regulation system between insulin action and secretion fails, resulting in abnormally high blood glucose levels (Nguyen & Le, 2012; Sharma et al., 2021). Several investigations have aimed to identify compounds that can be used in diabetes therapy, particularly those that enhance insulin action on target tissues and restore pancreatic β-cell function.

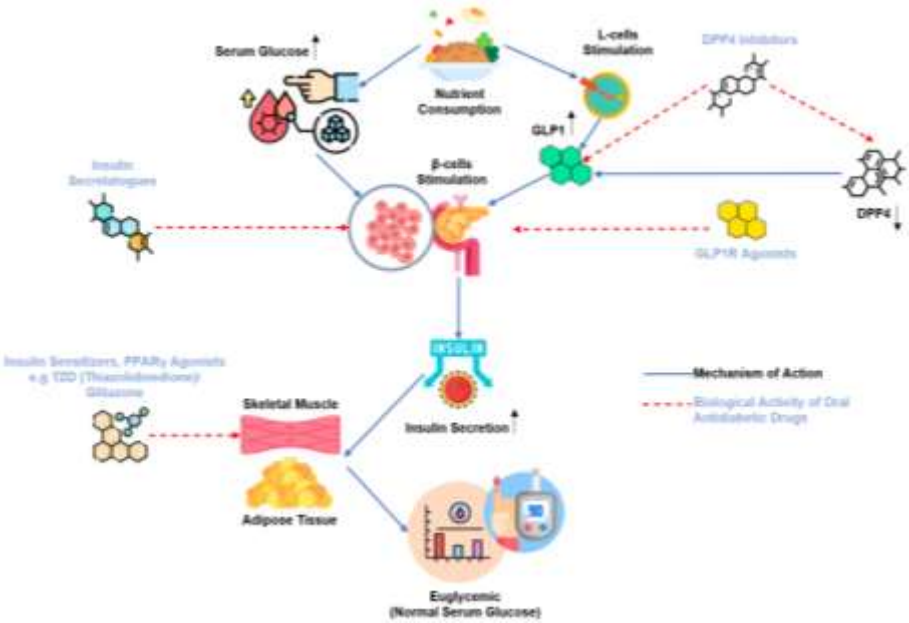


**Figure 1.** Structure of several oral antidiabetic drugs and their treatment targets

Kanwal et al. (2022) identified four main types of diabetes treatment targets primarily related to hormonal regulation, including processes associated with insulin secretion, tissue sensitivity to insulin, and inhibition of intestinal glucose absorption (Figure 1).

### 1. Insulin Secretagogues

Insulin secretagogues stimulate pancreatic β-cells to secrete more insulin. There are two types of insulin secretagogues: sulfonylureas and non-sulfonylureas. Both types increase insulin secretion and reduce the risk of microvascular complications. Sulfonylureas bind to sulfonylurea receptors on pancreatic β-cells and stimulate insulin secretion. Despite their disadvantage of prolonged binding to β-cells, they can induce extended insulin release. Non-sulfonylureas also stimulate insulin secretion from β-cells but act for a shorter duration.

The five potential mechanisms for activating β-cell metabolism related to insulin secretion include: blocking β-cell KATP channels; increasing intracellular $Ca^{2+}$ concentration independently of KATP channels; activating various transduction pathways that enhance β-cell activity in insulin secretion; acting on β-cell membrane receptors; and acting on β-cell nuclear receptors (Nguyen & Le, 2012; Sharma et al., 2021).

### 2. Insulin Mimetics

Insulin mimetics are agents that help lower blood glucose levels by activating glucose transporters in muscle and adipose cells, thereby mimicking the function of insulin.

### 3. Insulin Sensitizers

Insulin sensitizers enhance the sensitivity of body tissues to insulin. These agents have also been shown to improve various cardiac risk factors, such as reducing the risk of blood clots, high blood pressure, abnormal lipid profiles, elevated C-reactive protein levels, unwanted lipoproteins, serum fibrinogen, and even abnormal thickening of the heart muscle (Sharma et al., 2021).

### 4. Starch Blockers

Another critical treatment target for controlling diabetes is the inhibition of glucose absorption in the small intestine. This involves inhibiting the activity of proteins that influence glucose metabolism and absorption, such as α-glucosidase, dipeptidyl peptidase-4 (DPP-4), and sodium-glucose co-transporter type 2 (SGLT2) (Sharma et al., 2021).

## 2) Human Islet Amyloid Polypeptide (hIAPP) to Improve Pancreatic β-Cell Function

The misfolding and aggregation of human islet amyloid polypeptide (hIAPP), also known as amylin, are implicated in the progressive decline of pancreatic β-cell function and mass under hyperglycemic conditions. hIAPP may mediate pancreatic β-cell dysfunction and apoptosis through mechanisms such as endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, inflammatory cytokine secretion, and autophagy blockade. Thus, further investigation into the hIAPP aggregation pathway as a potential therapeutic target is essential for diabetes management (Roham et al., 2022).

### I. Pathophysiology of hIAPP-Related Pancreatic β-Cell Damage

The hIAPP is synthesized as a prepropeptide consisting of 89 amino acids. This prepropeptide undergoes proteolytic processing in the endoplasmic reticulum to form a 67-amino acid propeptide, which is then post-translationally modified to yield the mature 37-amino acid hIAPP peptide. Hyperglycemic conditions can lead to the overproduction and hypersecretion of hIAPP, inhibiting insulin secretion through autocrine effects. Under diabetic conditions, hIAPP can misfold and form aggregates, oligomers, and fibrils, which deposit as plaques in the islets of Langerhans. These hIAPP deposits are also found in red blood cells and other critical organs such as the heart, kidneys, brain, and eyes. The aggregates can exacerbate disease progression; for example, their interaction with beta-amyloid (Aβ) peptides can induce brain aggregation, leading to diabetes-related dementia. Additionally, hIAPP aggregates can contribute to the development of diabetic nephropathy (Roham et al., 2022).

The hIAPP-induced oxidative stress triggers the c-Jun NH2-terminal kinase (JNK) pathway by activating apoptosis signal-regulating kinase-I (ASK1), leading to the engagement of various proapoptotic molecules. The hIAPP oligomers induce IL-1β secretion from macrophages, causing islet inflammation. Moreover, hIAPP increases the expression of other inflammatory cytokines such as chemokine (C-C motif) ligand 2 (CCL2), tumor necrosis factor-α, IL-1α, IL-6, CCL3, chemokine C-X-C motif ligand (CXCL)1, CXCL2, and CXCL10, as well as inflammasome markers such as NACHT, LRR, and PYD domain-containing protein 3 (Nlrp3), PYD and CARD domains, and caspase 1. These pathways collectively result in heightened inflammatory reactions, apoptosis, and pancreatic β-cell damage through the induction of endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, inflammatory cytokine secretion, and autophagy blockade (Roham et al., 2022).

### 2. hIAPP as a Treatment Target to Improve Pancreatic β-Cell Function

Hyperglycemia can induce the misfolding, oligomer formation, and aggregation of hIAPP, exacerbating diabetic conditions associated with pancreatic β-cell damage and dysfunction. The deposition of amyloid hIAPP aggregates in islet cells is a major factor causing pancreatic islet damage through increased oxidative stress and activation of various proinflammatory and proapoptotic molecules. Therefore, targeting the hIAPP aggregation pathway and developing

hIAPP aggregation inhibitors are promising therapeutic strategies for controlling and potentially reversing diabetes.

### 3) Inhibition of α-Glucosidase, DPP-4 (Dipeptidyl Peptidase-4), and SGLT2 (Sodium Glucose Co-transporter Type-2)

Current diabetes treatment strategies necessitate further investigation and development. One potential treatment target is the modulation of the incretin pathway, which can enhance insulin secretion—a hormone crucial for reducing hyperglycemia and maintaining glucose homeostasis. Incretin pathway modulators include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1R) agonists, and sodium glucose co-transporter type 2 (SGLT2) inhibitors (Borah et al., 2022). GLP-1, a gastrointestinal hormone that stimulates insulin secretion, exhibits several beneficial effects, including hypoglycemic, anti-proteinuria, anti-fibrotic, anti-hypertensive, and anti-obesity properties (Kim & Park, 2017). GLP-1 is rapidly degraded by DPP-4 in the renal proximal tubules and podocytes, leading to increased oxidative stress and inflammatory factor release. Thus, DPP-4 inhibitors, in conjunction with GLP-1 receptor agonists, are vital targets for diabetes treatment and the management of its complications. Additionally, SGLT2 inhibitors are essential for reducing sodium and glucose reabsorption in the proximal tubules, thereby increasing their excretion in the urine and preventing glomerular hyperfiltration and albuminuria associated with diabetic nephropathy (Keri et al., 2018). The following sections detail the modulation of the incretin pathway mediated by α-glucosidase inhibitors, DPP-4 inhibitors, and SGLT2 inhibitors.

#### 1. α-Glucosidase Inhibitors

An important target in diabetes management involves inhibiting the activity of the α-glucosidase enzyme, which plays a crucial role in carbohydrate metabolism and cellular glucose absorption. α-Glucosidase, secreted in the small intestine, catalyzes the breakdown of oligosaccharides and disaccharides into monosaccharides such as glucose, thereby increasing glucose concentration in the body (Abbas et al., 2019). The most commonly used α-glucosidase inhibitors are acarbose and miglitol. Acarbose slows carbohydrate metabolism and reduces postprandial plasma glucose spikes. Additionally, acarbose administration increases fibroblast growth factor 21 (FGF21) and decreases insulin-like growth factor-I (IGF-I), contributing to the upregulation of GLP-1 (Glucagon-like peptide-1), which enhances insulin secretion and reduces blood glucose levels (McCarty & DiNicolantonio, 2015).

#### 2. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Dipeptidyl peptidase-4 (DPP-4) is present on various cell types, including renal proximal tubular cells and endothelial cells. During diabetes and inflammatory responses leading to glomerulosclerosis, DPP-4 expression is upregulated (Borah et al., 2022; Hocher et al., 2012). Inhibiting DPP-4 enzyme activity affects glucose metabolism and absorption, primarily by increasing GLP-1 levels.

GLP-1 is expressed in adipose tissue following food intake, delaying gastric emptying, enhancing insulin secretion, and reducing glucagon secretion (Kanwal et al., 2022). As an incretin and gastrointestinal hormone, GLP-1 increases insulin release. Its receptor, GLP-1R, is located in proximal tubular cells and preglomerular vascular smooth muscle cells, belonging to the G protein-coupled receptor (GPCR) family (Nauck & Meier, 2018; Pyke et al., 2014). GLP-1, secreted by enteroendocrine L cells, slows gastric emptying, suppresses appetite, promotes pancreatic β-cell proliferation, and induces insulin secretion (Borah et al., 2022). Additionally, GLP-1 inhibits glucagon secretion, limiting hyperglycemia from endogenous glucose production. However, GLP-1 is rapidly degraded by DPP-4, resulting in a very short plasma half-life (1-2 minutes). Inhibiting

DPP-4 significantly enhances GLP-1's insulinotropic effects (Méndez et al., 2020; Müller et al., 2019; Sharma et al., 2021).

Several GLP-1 analogs, such as exenatide, lixisenatide, albiglutide, dulaglutide, liraglutide, and semaglutide, have been identified. GLP-1 or GLP-1R receptor agonists derived from medicinal plant extracts can minimize disease risk by inducing hypoglycemia, reducing food intake, and promoting weight loss (Borah et al., 2022) (Figure 2).

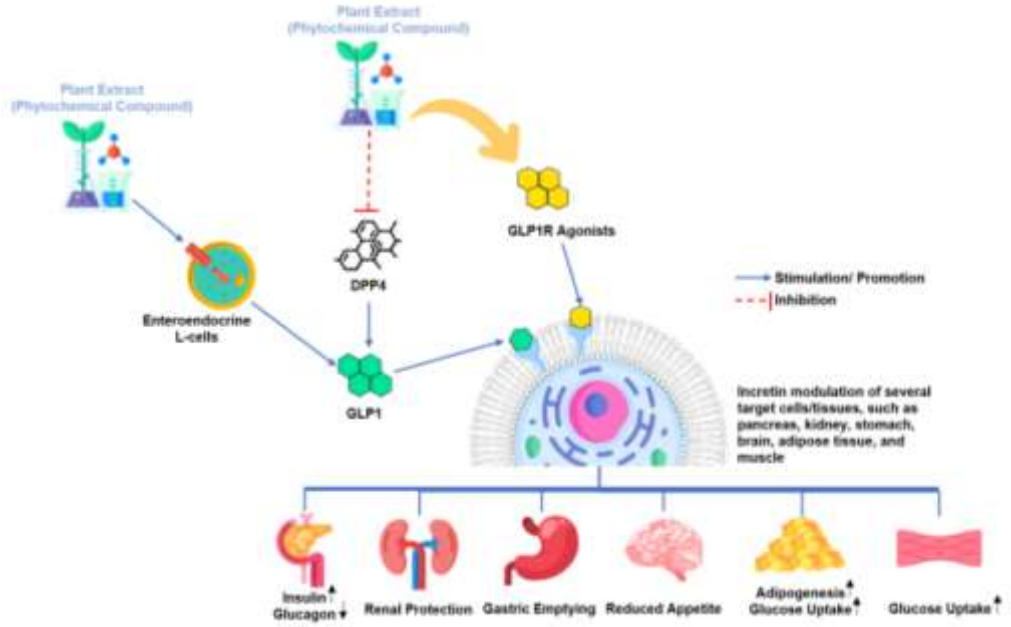


**Figure 2.** Incretin modulation of GLP-1 analog or GLP-1R agonist induced phytochemical compounds in plant extracts

### 3. Sodium Glucose Co-Transporter Type 2 (SGLT2) Inhibitors

Sodium-glucose cotransporters (SGLTs) and glucose transporters (GLUTs) are actively and passively involved in glucose transport, respectively. There are six types of SGLTs that facilitate glucose transport in the body. Among these, SGLT2, located in the proximal tubule of the kidney, plays a crucial role in maintaining glucose homeostasis. SGLT2 is considered a more promising diabetes treatment target than SGLT1 (Sharma et al., 2021). Under hyperglycemic conditions, increased reabsorption of glucose and sodium via SGLT2 in the proximal tubule can reduce distal sodium delivery to the macula densa, a group of specialized cells lining the distal tubule wall adjacent to the juxtaglomerular cells. This enhanced SGLT2 activity causes glomerular hyperfiltration, potentially leading to the pathological development of diabetic complications such as diabetic nephropathy (Keri et al., 2018).

Inhibiting SGLT2 can significantly reduce glucose and sodium reabsorption in tubular cells, thereby increasing glucose excretion in the urine and lowering blood glucose levels (Borah et al., 2022). Most SGLT2 inhibitors work by inhibiting SGLT2 at the renal proximal convoluted tubule (PCT) site, reducing glucose reabsorption in the proximal tubule and facilitating glucose elimination through urine (Vallon, 2015). Clinically, SGLT2 inhibitors also offer protective effects on the cardiovascular system and kidneys (Ni et al., 2020). These agents act independently of insulin signaling, promoting increased glucose excretion by the kidneys (Kanwal et al., 2022) (Figure 3).

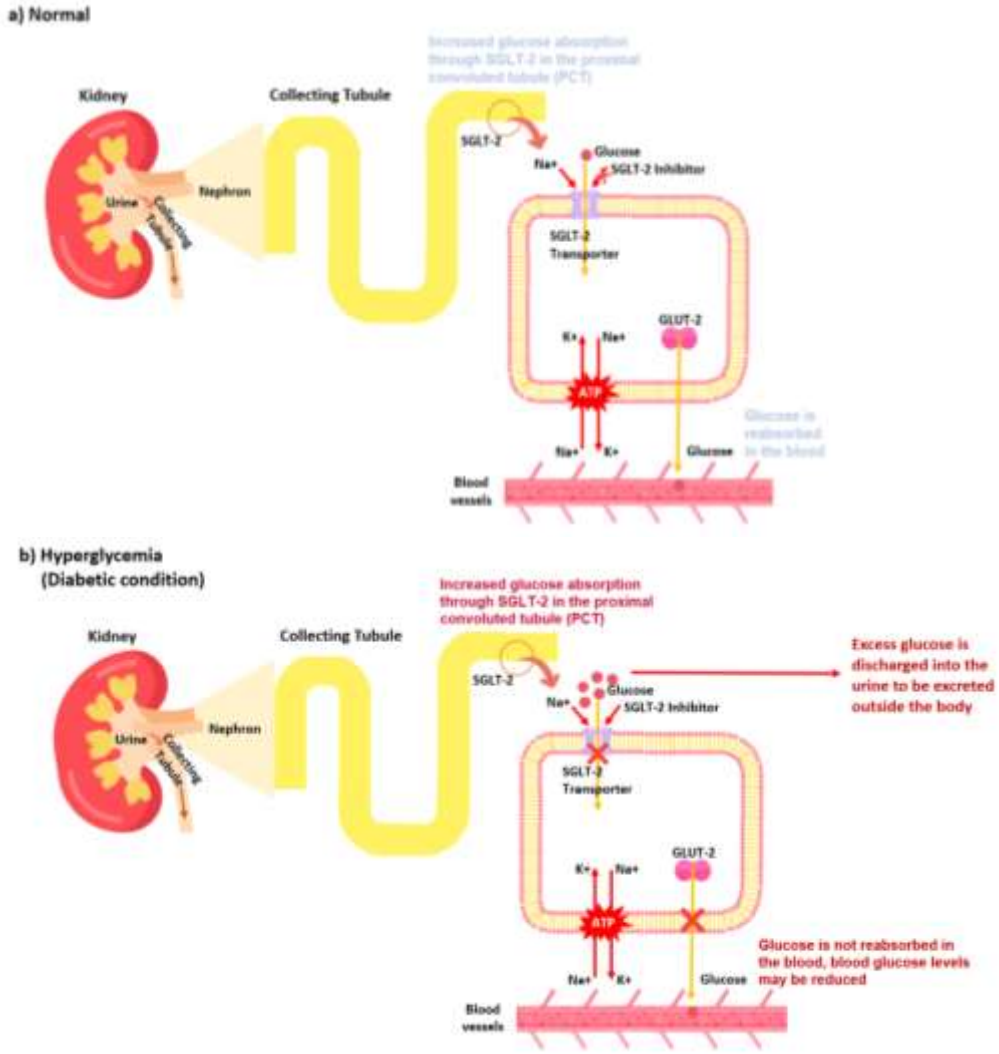


**Figure 3.** Mechanism of action of SGLT2 inhibitors (a) Normal pathway (b) Diabetes-related pathway

## 4) GLUT4 Translocation to Induce Normoglycemia

Glucose serves as a primary energy source, converted into ATP (adenosine triphosphate) through cellular respiration. The transport of glucose into cells is typically facilitated by a family of glucose-specific transport proteins known as glucose transporters, which enable glucose to traverse the cell membrane via facilitated diffusion (Bryant et al., 2002).

The endocrine hormone insulin plays a pivotal role in regulating glucose homeostasis in the body by stimulating physiological responses in its target tissues to control blood glucose levels. In skeletal muscle and adipose tissue, insulin-mediated glucose transport is primarily facilitated by the GLUT4 glucose transporter. GLUT4 is a 12-transmembrane protein that assists in the transfer of peripheral blood glucose into cells across the plasma membrane. This transport process follows a low concentration gradient and does not require ATP, classifying it as facilitated diffusion (Satoh, 2014). Bryant et al. (2002) demonstrated that in muscle and adipose cells, insulin stimulates the translocation of GLUT4 from its intracellular compartments to the cell surface, thereby facilitating the reduction of plasma glucose levels. This process is known as GLUT4 translocation.

During GLUT4 translocation, insulin triggers tyrosine phosphorylation on IRS (insulin receptor substrate), which activates PI3K (phosphoinositide 3-kinase). PI3K then catalyzes the conversion of PI (4,5) P2 to PI (3,4,5) P3, subsequently enhancing the activity of PDK1 and

PDK2 (phosphoinositide-dependent kinases). These kinases phosphorylate and activate AKT (protein kinase B), which in turn phosphorylates AS160 (Akt substrate of 160 kDa). AS160 negatively regulates GLUT4 translocation by converting the GTP-bound active form of Rab proteins to the GDP-bound inactive form. The inhibition of AS160 induces the translocation of GLUT4 storage vesicles (GSV) to the plasma membrane. Following this, the GLUT4 molecules are inserted into the plasma membrane through a fusion process, facilitated by insulin, which stimulates the exocytosis process, thereby dispersing GLUT4 molecules within the plasma membrane (Yang, 2010) (Figure 4).

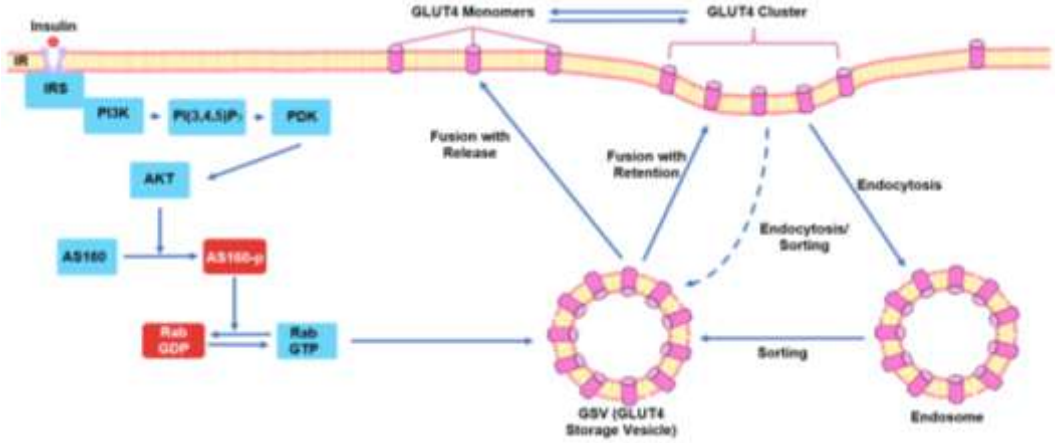


Figure 4. GLUT4 translocation

Insulin signaling that regulates GLUT4 translocation is mediated through the PI3K pathway and the Rho family TC10 GTPase pathway. Additionally, the AMPK (5'adenosine monophosphate-activated protein kinase) pathway also mediates GLUT4 translocation. In mammalian cells, AMPK is activated by an increase in the AMP/ATP ratio, serving as an energy sensor. This increase in AMPK can be induced by muscle cell contraction/exercise and the administration of compounds such as metformin (Lee et al., 2012; Yang, 2010). Consequently, glucose homeostasis is maintained through the regulation of GLUT4 translocation, enabling glucose transport into target cells, particularly muscle cells, which store approximately 75% of excess glucose in the body. This process helps mitigate hyperglycemia and prevent diabetic complications.

### 5) RNA-Binding Proteins as Mediators of Protein Expression in Post-Transcriptional Mechanisms Related to the Development of Diabetic Complications

The RNA-binding proteins (RBPs) play a crucial role as post-transcriptional regulators, influencing gene expression through mechanisms such as alternative splicing, RNA export, mRNA translation, RNA degradation, and RNA stabilization. These proteins can mediate abnormal gene expression in diabetic conditions, thereby contributing to the development of associated disease complications (Chen et al., 2022).

Investigations by Chen et al. (2022) have revealed that RBPs are significantly involved in the progression of metabolic diseases, including hyperuricemia, hyperlipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), and diabetes. For instance, the RNA-binding protein fox-1 homolog 2 (RBFOX-2) is implicated in coronary heart disease by binding to the GCAUG(U) motif in RNA to regulate alternative splicing. Additionally, HuR, another RBP, interacts with glucose transporter type-1 (GLUT1) mRNA, potentially mediating GLUT1-related post-transcriptional and metabolic disorders in diabetes. HuR is also believed to influence IL-6 mRNA by increasing its stabilization, thereby promoting an inflammatory response associated with diabetic complications.

Therefore, post-transcriptional modulation by RBPs may be a critical mechanism in the pathogenesis and progression of diabetes and its complications, highlighting RBPs as important therapeutic targets for further investigation.

### 6) Molecular Targets Involved in the Pathophysiology of Other Diabetes Complications

There are numerous novel therapeutic targets involved in the molecular pathways underlying the pathophysiology of diabetes. These targets are particularly relevant for the development of strategies to control and manage diabetes. Some of the key targets include 5'AMP-activated protein kinase (AMPK), fructose-1,6-bisphosphatase (FBPase), glucokinase, glycogen synthase kinase 3, pyruvate dehydrogenase complex (PDC), 11β-hydroxysteroid dehydrogenase (11β-HSD), glutamine fructose-6-phosphate amidotransferase (GFAT), and protein tyrosine phosphatase 1B (PTP1B). These targets are outlined in Table 1 below.

**Table 1.** Potential targets in diabetes treatment

| No | Target compound | Characteristics | Physiological role | Involvement in diabetes interventions | Reference |
|---|---|---|---|---|---|
| 1 | 5' AMP-activated protein kinase (AMPK) | AMPK has a catalytic subunit (α) and a regulatory subunit (β and γ), known as an energy sensor | AMPK accelerates increased fatty acid oxidation (lipolysis) in muscle and liver, β-oxidation, glycolysis, and glucose uptake. It also inhibits gluconeogenesis, glycogenesis, lipogenesis in the liver and adipose tissue, cholesterol biosynthesis, etc. | AMPK can increase glucose uptake and transport into cells by translocating GLUT4 vesicles from the cytoplasm to the cell membrane | (Garcia & Shaw, 2017; Sharma et al., 2021; Srivastava et al., 2012; Yu et al., 2010) |
| 2 | Fructose-1,6-bisphosphatase (FBPase) | FBPase enzymatically accelerates gluconeogenesis and is inhibited competitively by fructose-2,6-bisphosphate and allosterically by AMP | FBPase promotes endogenous glucose production through gluconeogenesis, leading to hyperglycemia that contributes to type 2 diabetes mellitus and its complications. | Lowering FBPase levels can reduce hyperglycemia symptoms, and its inhibition such as by metformin targeting the AMP binding site offers a potential treatment strategy. | (Hunter et al., 2018; Kaur et al., 2017; Liu & Zhang, 2018; Sharma et al., 2021) |
| 3 | Glucokinase (GCK) | Glucokinase, also known as hexokinase IV, catalyzes the phosphorylati | GCK plays a key role in glucose homeostasis, acting as a glucose sensor in pancreatic β-cells and as a gatekeeper in liver cells to promote | Inactivating mutations in glucokinase can cause hyperglycemia, while activating mutations may lead to hypoglycemia. Glucokinase activators | (Sharma et al., 2021; Zhu et al., 2018) |

| | | | | | |
|---|---|---|---|---|---|
| | | on of glucose to glucose-6-phosphate. | glycogen synthesis and lower blood glucose levels. | (GKAs) offer a promising therapeutic target for diabetes treatment. | |
| 4 | Glycogen synthase kinase 3 (GSK-3) | GSK-3 has two isomeric forms, GSK-3α and GSK-3ß | GSK-3 is a negative regulator of glycogen synthase, a glycosyltransferase that catalyzes glycogen chain elongation and glucose conversion to glycogen. It functions as a serine/threonine kinase that phosphorylates glycogen synthase and other substrates. | Overexpression of GSK-3 is linked to various pathological conditions. Its inhibition may serve as a therapeutic target by enhancing glycogen synthase activity and reducing glucose overload. | (Sharma et al., 2021) |
| 5 | Pyruvate dehydrogenase complex (PDC) | PDC is a multi-enzyme complex located in the inner mitochondrial membrane. The four PDK isoenzymes: PDK1, PDK2, PDK3, and PDK4, are involved in tissue-specific protein expression. | PDC catalyzes the oxidative decarboxylation of pyruvate, the end product of aerobic glycolysis, to acetyl coenzyme A, linking glycolysis to the Krebs cycle. It oxidizes nicotinamide adenine dinucleotide ($NAD^+$) to NADH and produces carbon dioxide. | PDK4, an isoenzyme expressed during diabetes, mast cell-mediated allergies, cancer proliferation, and starvation, can be targeted for inhibition to enhance glucose uptake and storage, thereby lowering blood glucose levels and preventing metabolic disorders. | (Lee et al., 2019; Lee, 2014; Sharma et al., 2021) |
| 6 | 11β-Hydroxysteroid dehydrogenase (11β-HSD) | 11β-HSD is an enzyme that catalyzes the conversion of inactive cortisol into its active form. | 11β-HSD catalyzes the conversion of inactive cortisol to its active form. | Elevated active glucocorticoid cortisol levels contribute to metabolic disorders like diabetes, obesity, dyslipidemia, and hypertension. Transgenic mice lacking 11β-hydroxysteroid dehydrogenase show increased insulin sensitivity and resistance to high-fat diet-induced obesity, suggesting that | (Cooper & Stewart, 2009; Kanwal et al., 2022) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | reducing this enzyme's expression may improve insulin sensitivity and prevent metabolic syndrome. | |
| 7 | Glutamine Fructose-6-Phosphate Amido Transferase (GFAT) | GFAT acts as a catalyst in the hexosamine biosynthesis pathway. | GFAT accelerates the hexosamine biosynthesis pathway, promoting insulin resistance and activating the production of certain growth factors. | Inhibiting GFAT can block the hexosamine biosynthesis pathway and help manage metabolic disorders related to type 2 diabetes mellitus. | (Kanwal et al., 2022; Schleicher & Weigert, 2000) |
| 8 | Protein Tyrosine Phosphatase 1B (PTP1B) | PTP1B is a negative regulator of insulin and leptin signaling, hormones involved in glucose metabolism and satiety. | PTP1B dephosphorylates tyrosine residues in the insulin receptor's activation segment, inhibiting insulin signaling and reducing insulin sensitivity. It also lowers tissue sensitivity to leptin, preventing satiety despite adequate energy stores. | PTP1B reduces pancreatic β-cell proliferation and insulin secretion in response to rising glucose levels. Conversely, inhibiting PTP1B can enhance insulin signaling, maintain metabolic balance, and increase insulin secretion. | (Fernandez-Ruiz et al., 2014; Kanwal et al., 2022) |
| 9 | Peroxisome Proliferator-Activated Receptor Gamma Co-Activator Alpha (PGC-1α) | PGC-1α is a protein encoded by the PPARGC1A gene | PGC-1α maintains energy homeostasis and regulates insulin signaling expression. It also supports mitochondrial biogenesis, dynamics, and antioxidant gene activation, helping prevent mitochondrial dysfunction and metabolic disorders linked to adipocyte damage. | Dysregulation of PGC-1α disrupts cellular homeostasis and worsens inflammation. In adipocyte dysfunction, reduced PGC-1α causes mitochondrial damage, leading to irritation, oxidative stress, and activation of the nuclear factor κB. Lower PGC-1α levels and mitochondrial dysfunction in adipose tissue contribute to obesity and insulin resistance. Enhancing PGC-1α function may improve adipose tissue health and benefit organs | (Kanwal et al., 2022; Kleiner et al., 2012; Wenz et al., 2009) |

like the liver.

| | | | | | |
|---|---|---|---|---|---|
| I0 | Peroksisom Proliferator-Activated Receptor Gama (PPARγ) | PPARγ is a positive regulator of adipogenesis, with high expression in adipose tissue and lower levels in various other tissues and cells. | PPARγ regulates adipogenesis and enhances insulin sensitivity, playing a key role in maintaining glucose homeostasis across various target cells and tissues. | Selective deletion of PPARγ in tissues like adipose, muscle, macrophages, and brain disrupts glucose homeostasis. PPARγ also enhances insulin sensitivity by stimulating adiponectin secretion, a key insulin-sensitizing hormone. | (Kanwal et al., 2022) |

Future studies integrating these molecular pathways could facilitate the development of multifunctional therapeutic agents.

## CONCLUSION

This review highlights four primary molecular approaches and two emerging aspects of diabetes intervention, encompassing hormonal regulation, human islet amyloid polypeptide (hIAPP) aggregation, incretin modulation, glucose transport mechanisms, RNA-binding proteins (RBPs), and key enzymatic pathways associated with glucose metabolism. A deeper understanding and further development of therapeutic strategies targeting these molecular pathways could substantially improve diabetes management, enhance insulin sensitivity, and prevent disease-related complications. This integrative molecular perspective provides a theoretical basis for designing novel multi-targeted interventions in diabetes therapy.

## REFERENCES

Abbas, G., Al Harrasi, A., Hussain, H., Hamaed, A., & Supuran, C. T. (2019). The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2). *Bioorganic Chemistry*, *86*, 305–315. Retrieved from https://doi.org/10.1016/j.bioorg.2019.02.009

Borah, A. K., Ahmed, S. A., & Borah, J. C. (2022). Phytomedicine as a source of SGLT2 inhibitors, GLP-1 secretagogues and DPP-IV inhibitors for mitigation of diabetic nephropathy. *Phytomedicine Plus*, *2*(2), 100225. Retrieved from https://doi.org/10.1016/j.phyplu.2022.100225

Bryant, N. J., Govers, R., & James, D. E. (2002). Regulated transport of the glucose transporter GLUT4. *Nature Reviews Molecular Cell Biology*, *3*(4), 267–277. Retrieved from https://doi.org/10.1038/nrm782

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. *Frontiers in Endocrinology*, *8*. Retrieved from https://doi.org/10.3389/fendo.2017.00006

Chen, X., Wu, J., Li, Z., Han, J., Xia, P., Shen, Y., Ma, J., Liu, X., Zhang, J., & Yu, P. (2022). Advances in the study of RNA-binding proteins in diabetic complications. *Molecular Metabolism*, *62*, 101515. Retrieved from https://doi.org/10.1016/j.molmet.2022.101515

Cooper, M. S., & Stewart, P. M. (2009). 11β-Hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. *The Journal of Clinical Endocrinology & Metabolism*, *94*(12), 4645–4654. Retrieved from https://doi.org/10.1210/jc.2009-1412

Djrolo, F., Paraïso, N. M., Diarra, O., & Makoutode, M. (2014). Diabetes complications and associated factors in type 2 diabetic patients in Cotonou. *Journal of Diabetes Mellitus*, *4*(04), 311. Retrieved from https://doi.org/10.4236/jdm.2014.44043

Fernandez-Ruiz, R., Vieira, E., Garcia-Roves, P. M., & Gomis, R. (2014). Protein tyrosine phosphatase-1B modulates pancreatic β-cell mass. *PLoS ONE*, *9*(2), e90344. Retrieved from https://doi.org/10.1371/journal.pone.0090344

Garcia, D., & Shaw, R. J. (2017). AMPK: Mechanisms of cellular energy sensing and restoration of metabolic balance. *Molecular Cell*, *66*(6), 789–800. Retrieved from https://doi.org/10.1016/j.molcel.2017.05.032

Gautier, J. F., Monguillon, P., Verier-Mine, O., Valensi, P., Fiquet, B., Dejager, S., & Charbonnel, B. (2016). Which oral antidiabetic drug to combine with metformin to minimize the risk of hypoglycemia when initiating basal insulin? *Diabetes Research and Clinical Practice*, *116*, 26–28. Retrieved from https://doi.org/10.1016/j.diabres.2016.04.008

Gjessing, H. J., Jørgensen, U. L., Møller, C. C., Pedersen, J., Grodum, E., & Schousboe, K. (2014). Better glycaemic outcome, low levels of acute severe complications, and high patient satisfaction in routine practice in type 1 diabetes treated with an insulin pump. *Journal of Diabetes Mellitus*, *04*(04), 304–310. Retrieved from https://doi.org/10.4236/jdm.2014.44042

Handorf, A. M., Sollinger, H. W., & Alam, T. (2015). Genetic engineering of surrogate β cells for treatment of type 1 diabetes mellitus. *Journal of Diabetes Mellitus*, *05*(04), 295–312. Retrieved from https://doi.org/10.4236/jdm.2015.54037

Hocher, B., Reichetzeder, C., & Alter, M. L. (2012). Renal and cardiac effects of DPP4 inhibitors–from preclinical development to clinical research. *Kidney and Blood Pressure Research*, *36*(1), 65–84. Retrieved from https://doi.org/10.1159/000339028

Hunter, R. W., Hughey, C. C., Lantier, L., Sundelin, E. I., Peggie, M., Zeqiraj, E., Sicheri, F., Jessen, N., Wasserman, D. H., & Sakamoto, K. (2018). Metformin reduces liver glucose production by inhibition of fructose-1-6-bisphosphatase. *Nature Medicine*, *24*(9), 1395–1406. Retrieved from https://doi.org/10.1038/s41591-018-0159-7

International Diabetes Federation. (2000). *Diabetes atlas 2000* (1st ed.). International Diabetes Federation. Retrieved from https://diabetesatlas.org/atlas/first-edition/

International Diabetes Federation. (2013). *IDF diabetes atlas* (6th ed.). International Diabetes Federation. Retrieved from https://diabetesatlas.org/atlas/sixth-edition/

International Diabetes Federation. (2015). *IDF diabetes atlas* (7th ed.). International Diabetes Federation. Retrieved from https://diabetesatlas.org/atlas/seventh-edition/

International Diabetes Federation. (2019). *IDF diabetes atlas* (9th ed.). International Diabetes Federation. Retrieved from https://diabetesatlas.org/atlas/ninth-edition/

Kanwal, A., Kanwar, N., Bharati, S., Srivastava, P., Singh, S. P., & Amar, S. (2022). Exploring new drug targets for type 2 diabetes: Success, challenges and opportunities. *Biomedicines*, *10*(2), 331. Retrieved from https://doi.org/10.3390/biomedicines10020331

Kaur, R., Dahiya, L., & Kumar, M. (2017). Fructose-1,6-bisphosphatase inhibitors: A new valid approach for management of type 2 diabetes mellitus. *European Journal of Medicinal Chemistry*, *141*, 473–505. Retrieved from https://doi.org/10.1016/j.ejmech.2017.09.029

Keri, K. C., Samji, N. S., & Blumenthal, S. (2018). Diabetic nephropathy: newer therapeutic perspectives. *Journal of Community Hospital Internal Medicine Perspectives*, *8*(4), 200–207. Retrieved from https://doi.org/10.1080/20009666.2018.1500423

Kerru, N., Singh-Pillay, A., Awolade, P., & Singh, P. (2018). Current anti-diabetic agents and their molecular targets: A review. *European Journal of Medicinal Chemistry*, *152*, 436–488. Retrieved from https://doi.org/10.1016/j.ejmech.2018.04.061

Kim, Y., & Park, C. W. (2017). New therapeutic agents in diabetic nephropathy. *The Korean Journal of Internal Medicine*, *32*(1), 11–25. Retrieved from https://doi.org/10.3904/kjim.2016.174

King, G. L., Park, K., & Li, Q. (2016). Selective insulin resistance and the development of cardiovascular diseases in diabetes: The 2015 edwin bierman award lecture. *Diabetes*, *65*(6), 1462–1471. Retrieved from https://doi.org/10.2337/db16-0152

Kleiner, S., Mepani, R. J., Laznik, D., Ye, L., Jurczak, M. J., Jornayvaz, F. R., Estall, J. L., Chatterjee Bhowmick, D., Shulman, G. I., & Spiegelman, B. M. (2012). Development of insulin resistance in mice lacking PGC-1α in adipose tissues. *Proceedings of the National Academy of Sciences*, *109*(24), 9635–9640. Retrieved from https://doi.org/10.1073/pnas.1207287109

Kobayashi, M., Tsukube, S., Ikeda, Y., & Shuto, Y. (2014). Safety and efficacy of combination therapy with insulin glargine and oral hypoglycaemic agents including DPP-4 inhibitors in Japanese T2DM patients: ALOHA 2 study, a post-marketing surveillance for Lantus®. *Journal of Diabetes Mellitus*, *4*(04), 273–289. Retrieved from https://doi.org/10.4236/jdm.2014.44039

Lee, D., Pagire, H. S., Pagire, S. H., Bae, E. J., Dighe, M., Kim, M., Lee, K. M., Jang, Y. K., Jaladi, A. K., Jung, K.-Y., Yoo, E. K., Gim, H. E., Lee, S., Choi, W.-I., Chi, Y.-I., Song, J. S., Bae, M. A., Jeon, Y. H., Lee, G.-H., … Ahn, J. H. (2019). Discovery of novel pyruvate dehydrogenase kinase 4 inhibitors for potential oral treatment of metabolic diseases. *Journal of Medicinal Chemistry*, *62*(2), 575–588. Retrieved from https://doi.org/10.1021/acs.jmedchem.8b01168

Lee, I.-K. (2014). The role of pyruvate dehydrogenase kinase in diabetes and obesity. *Diabetes & Metabolism Journal*, *38*(3), 181–186. Retrieved from https://doi.org/10.4093/dmj.2014.38.3.181

Lee, J. O., Lee, S. K., Kim, J. H., Kim, N., You, G. Y., Moon, J. W., Kim, S. J., Park, S. H., & Kim, H. S. (2012). Metformin regulates glucose transporter 4 (GLUT4) translocation through AMP-activated protein kinase (AMPK)-mediated Cbl/CAP signaling in 3T3-L1 preadipocyte cells. *Journal of Biological Chemistry*, *287*(53), 44121–44129. Retrieved from https://doi.org/https://doi.org/10.1074/jbc.M112.361386

Liu, G.-M., & Zhang, Y.-M. (2018). Targeting FBPase is an emerging novel approach for cancer therapy. *Cancer Cell International*, *18*(1), 36. Retrieved from https://doi.org/10.1186/s12935-018-0533-z

Luo, T., Nocon, A., Fry, J., Sherban, A., Rui, X., Jiang, B., Xu, X. J., Han, J., Yan, Y., & Yang, Q. (2016). AMPK activation by metformin suppresses abnormal extracellular matrix remodeling in adipose tissue and ameliorates insulin resistance in obesity. *Diabetes*, *65*(8), 2295–2310. Retrieved from https://doi.org/10.2337/db15-1122

Mansour, M., Salam, R. F., Rashed, L., & Salam, H. (2014). Role of toll receptors in diabetic nephropathy. *Journal of Diabetes Mellitus*, *4*(01), 26–32. Retrieved from https://doi.org/10.4236/jdm.2014.41005

McCarty, M. F., & DiNicolantonio, J. J. (2015). Acarbose, lente carbohydrate, and prebiotics promote metabolic health and longevity by stimulating intestinal production of GLP-1. *Open Heart*, *2*(1), e000205. Retrieved from https://doi.org/10.1136/openhrt-2014-000205

Méndez, M., Matter, H., Defossa, E., Kurz, M., Lebreton, S., Li, Z., Lohmann, M., Löhn, M., Mors, H., Podeschwa, M., Rackelmann, N., Riedel, J., Safar, P., Thorpe, D. S., Schäfer, M., Weitz, D., & Breitschopf, K. (2020). Design, synthesis, and pharmacological evaluation of potent positive allosteric modulators of the glucagon-like peptide-1 receptor (GLP-1R). *Journal of Medicinal Chemistry*, *63*(5), 2292–2307. Retrieved from https://doi.org/10.1021/acs.jmedchem.9b01071

Müller, T. D., Finan, B., Bloom, S. R., D'Alessio, D., Drucker, D. J., Flatt, P. R., Fritsche, A., Gribble, F., Grill, H. J., Habener, J. F., Holst, J. J., Langhans, W., Meier, J. J., Nauck, M. A., Perez-Tilve, D., Pocai, A., Reimann, F., Sandoval, D. A., Schwartz, T. W., .. & Tschöp, M. H. (2019). Glucagon-like peptide 1 (GLP-1). *Molecular Metabolism*, *30*, 72–130. Retrieved from https://doi.org/10.1016/j.molmet.2019.09.010

Nauck, M. A., & Meier, J. J. (2018). Incretin hormones: Their role in health and disease. *Diabetes, Obesity and Metabolism*, *20*(SI), 5–21. Retrieved from https://doi.org/10.1111/dom.13129

Nguyen, N. D. T., & Le, L. T. (2012). Targeted proteins for diabetes drug design. *Advances in Natural Sciences: Nanoscience and Nanotechnology*, *3*(1), 013001. Retrieved from https://doi.org/10.1088/2043-6262/3/1/013001

Ni, L., Yuan, C., Chen, G., Zhang, C., & Wu, X. (2020). SGLT2i: Beyond the glucose-lowering effect. *Cardiovascular Diabetology*, *19*(1), 98. Retrieved from https://doi.org/10.1186/s12933-020-01071-y

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *Journal of Physiology and Pathophysiology*, *4*(4), 46–57. Retrieved from https://doi.org/10.5897/JPAP2013.0001

Penumathsa, S. V., Thirunavukkarasu, M., Zhan, L., Maulik, G., Menon, V. P., Bagchi, D., & Maulik, N. (2008). Resveratrol enhances GLUT-4 translocation to the caveolar lipid raft fractions through AMPK/Akt/eNOS signalling pathway in diabetic myocardium. *Journal of Cellular and Molecular Medicine*, *12*(6a), 2350–2361. Retrieved from https://doi.org/10.1111/j.1582-4934.2008.00251.x

Pyke, C., Heller, R. S., Kirk, R. K., Ørskov, C., Reedtz-Runge, S., Kaastrup, P., Hvelplund, A., Bardram, L., Calatayud, D., & Knudsen, L. B. (2014). GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*, *155*(4), 1280–1290. Retrieved from https://doi.org/10.1210/en.2013-1934

Ramesh, R., AdhishwarKumaran, N., KuzhandaiVelu, V., Reeta, R., SathishBabu, M., & Niranjan, G. (2015). Association between hepato-biliary status and HbA1c in type 2 diabetes mellitus with coronary artery disease (CAD). *Journal of Diabetes Mellitus*, *5*(02), 67–71. Retrieved from https://doi.org/10.4236/jdm.2015.52008

Roham, P. H., Save, S. N., & Sharma, S. (2022). Human islet amyloid polypeptide: A therapeutic target for the management of type 2 diabetes mellitus. *Journal of Pharmaceutical Analysis*, *12*(4), 556–569. Retrieved from https://doi.org/10.1016/j.jpha.2022.04.001

Satoh, T. (2014). Molecular mechanisms for the regulation of insulin-stimulated glucose uptake by small guanosine triphosphatases in skeletal muscle and adipocytes. *International Journal of Molecular Sciences*, *15*(10), 18677–18692. Retrieved from https://doi.org/10.3390/ijms151018677

Schleicher, E. D., & Weigert, C. (2000). Role of the hexosamine biosynthetic pathway in diabetic nephropathy. *Kidney International*, *58*, S13–S18. Retrieved from https://doi.org/10.1046/j.1523-1755.2000.07703.x

Shalan, N., Al-Bazzaz, A., Al-Ani, I., Najem, F., & Al-Masri, M. (2015). Effect of carbon dioxide therapy on diabetic foot ulcer. *Journal of Diabetes Mellitus*, *05*(04), 284–289. Retrieved from https://doi.org/10.4236/jdm.2015.54035

Sharma, P., Singh, S., Thakur, V., Sharma, N., & Grewal, A. S. (2021). Novel and emerging therapeutic drug targets for management of type 2 Diabetes Mellitus. *Obesity Medicine*, *23*, 100329. Retrieved from https://doi.org/10.1016/j.obmed.2021.100329

Shroff, G. (2015a). A scoring system to assess patients with diabetes: Nutech functional score. *Journal of Diabetes Mellitus*, *5*(04), 245–251. Retrieved from https://doi.org/10.4236/jdm.2015.54030

Shroff, G. (2015b). Use of human embryonic stem cells in the treatment of diabetes mellitus: A case series. *Journal of Diabetes Mellitus*, *05*(04), 313–318. Retrieved from https://doi.org/10.4236/jdm.2015.54038

Spangler, J. G., & Kirk, J. (2014). Correlation between diabetes prevalence and subsequent cancer mortality in North Carolina counties. *Journal of Diabetes Mellitus*, *4*(01), 1–5. Retrieved from https://doi.org/10.4236/jdm.2014.41001

Srivastava, R. A. K., Pinkosky, S. L., Filippov, S., Hanselman, J. C., Cramer, C. T., & Newton, R. S. (2012). AMP-activated protein kinase: An emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *Journal of Lipid Research*, *53*(12), 2490–2514. Retrieved from https://doi.org/10.1194/jlr.R025882

Sumitani, S., Morita, S., Deguchi, R., Hirai, K., Mukai, K., Utsu, Y., Miki, S., Sato, B., Nakamura, H., & Kasayama, S. (2014). Improved β-cell function rather than increased insulin sensitivity is associated with reduction in hemoglobin A1c in newly diagnosed type 2 diabetic patients treated with metformin. *Journal of Diabetes Mellitus*, *4*(01), 44–49. Retrieved from https://doi.org/10.4236/jdm.2014.41008

Vallon, V. (2015). The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annual Review of Medicine*, *66*(1), 255–270. Retrieved from https://doi.org/10.1146/annurev-med-051013-110046

Wenz, T., Rossi, S. G., Rotundo, R. L., Spiegelman, B. M., & Moraes, C. T. (2009). Increased muscle PGC-1α expression protects from sarcopenia and metabolic disease during aging. *Proceedings of the National Academy of Sciences*, *106*(48), 20405–20410. Retrieved from https://doi.org/10.1073/pnas.0911570106

Yang, J. (2010). Role of clusters in insulin-regulated GLUT4 trafficking in adipose cells: A new paradigm? *International Journal of Biological Sciences*, *6*(7), 716–718. Retrieved from https://doi.org/10.7150/ijbs.6.716

Yu, L.-F., Qiu, B.-Y., Nan, F.-J., & Li, J. (2010). AMPK activators as novel therapeutics for type 2 diabetes. *Current Topics in Medicinal Chemistry*, *10*(4), 397–410. Retrieved from https://doi.org/10.2174/156802610790980611

Zhou, Q., Yang, X., Xiong, M., Xu, X., Zhen, L., Chen, W., Wang, Y., Shen, J., Zhao, P., & Liu, Q.-H. (2016). Chloroquine increases glucose uptake via enhancing GLUT4 translocation and fusion with the plasma membrane in L6 cells. *Cellular Physiology and Biochemistry*, *38*(5), 2030–2040. Retrieved from https://doi.org/10.1159/000445562

Zhu, X., Zhu, D., Li, X., Li, Y., Jin, X., Hu, T., Zhao, Y., Li, Y., Zhao, G., Ren, S., Zhang, Y., Ding, Y., & Chen, L. (2018). Dorzagliatin (HMS5552), a novel dual-acting glucokinase activator, improves glycaemic control and pancreatic β-cell function in patients with type 2 diabetes: A 28-day treatment study using biomarker-guided patient selection. *Diabetes, Obesity and Metabolism, 20*(9), 2113–2120. Retrieved from https://doi.org/10.1111/dom.13338