Chapter

Molecular Basis of Blood Glucose Regulation

Asma Ahmed and Noman Khalique

Abstract

Blood glucose level is regulated by multiple pancreatic hormones, which regulate it by different pathways in normal and abnormal conditions by expressing or suppressing multiple genes or molecular or cellular targets. Multiple synthetic drugs and therapies are used to cure glucose regulatory problems, while many of them are used to cure other health issues, which arise due to disturbance in blood glucose regulations. Many new approaches are used for the development of phytochemical-based drugs to cure blood glucose regulation problems, and many of the compounds have been isolated and identified to cure insulin resistance or regulate beta cell function or glucose absorption in the guts or GLP-1 homoeostasis or two/more pathways (e.g., either cure hyperglycemia or raise insulin resistance or cure pancreatic beta cell regeneration or augmentation of GLP-1, production of islet cell, production and increased insulin receptor signaling and insulin secretion or decreased insulin tolerance or gluconeogenesis and insulin-mimetic action or production of α-glucosidase and α-amylase inhibitor or conserve islet mass or activate protein kinase A (PKA) and extracellular signal regulated kinases (ERK) or activate AMPK and reduce insulin sensitivity or suppress α-glucosidase activity and activate AMPK and downstream molecules or prevents cell death of pancreatic β-cell and activates SIRT1 or lower blood glucose due to their insulin-like chemical structures or decrease lipid peroxidation.

Keywords: genes, molecular and cellular targets, hormones, pathways

1. Introduction

Blood glucose is regulated by the pancreatic hormones alone or in combination with other endocrine glands and all this is controlled by one or more gene or cellular or molecular targets. If any problem occurs in the normal pathway(s), then multiple drugs or therapies are used to cure it. Moreover with the emerging technologies, multiple plant based formulations has been synthesized or in process to cure all blood glucose regulation problems and their associated diseases.

2. Hormones for the regulation of blood glucose levels

2.1 Pancreas: an exocrine and endocrine organ

2.1.1 Location

It is located at the back of stomach, within left upper abdominal cavity.

2.1.2 Parts

Its parts are head, body and tail. Majority of this secretory organ consists of:

a. **Acinar/exocrine cells**: Which secrete pancreatic juice (containing digestive enzymes i.e. amylase, pancreatic lipase and trypsinogen) into main and accessory pancreatic duct.

b. **Endocrine cells**: Which secrete pancreatic hormones directly in blood stream (in endocrine way). These cells cluster together and form the so-called islets of Langerhans (small, island-like structures within the exocrine pancreatic tissue and accounts for only 1–2% of the entire organ) (**Figure 1**). These are five different types of cells and release various hormones [1]:

   i. **Glucagon-producing α-cells:** They are 15–20% of the total islet cells and releases Glucagon to increase blood glucose levels.

   ii. **Amylin-, C-peptide- and insulin-producing β-cells:** They are 65–80% of the total cells and produces insulin to decrease glucose.

   iii. **Pancreatic polypeptide (PP)-producing γ-cells:** 3–5% of the total islet cells, to regulate the exocrine and endocrine secretion activity of the pancreas, is made of them.

   iv. **Somatostatin-producing δ-cells:** Constitute 3–10% of the total cells and releases Somatostatin which inhibits both, glucagon and insulin release.

   v. **Ghrelin-producing ε-cells:** Comprise <1% of the total islet cells.

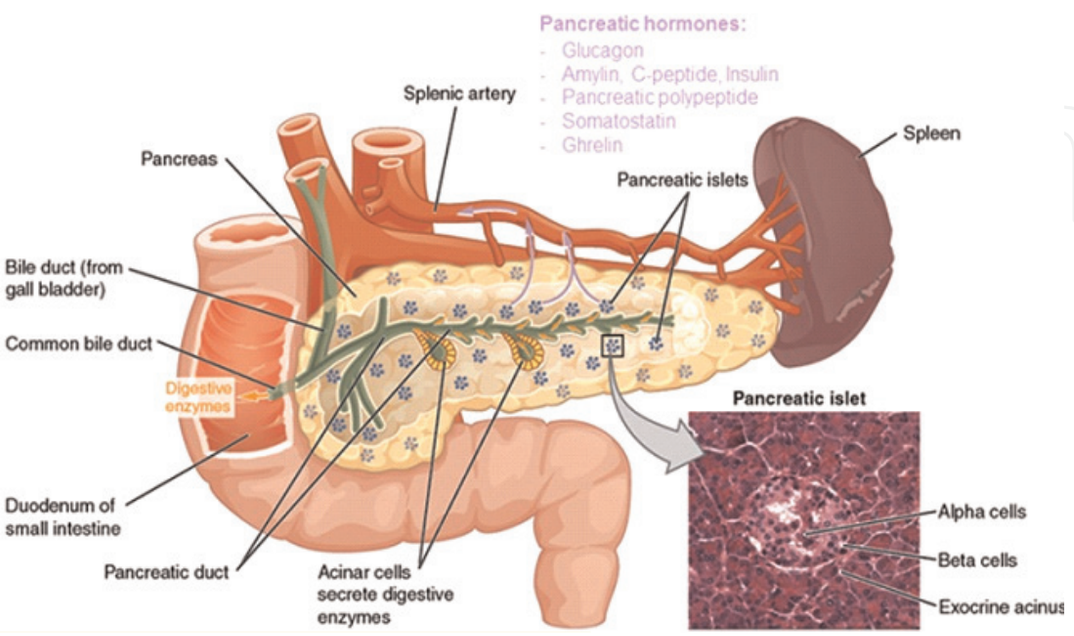


Figure 1.
Anatomical organization of the pancreas.

3. Pathways involved to regulate blood glucose levels in normal and abnormal conditions

Pancreas maintains blood glucose levels within a very narrow range (4–6 MM) through glucagon and insulin by their opposing and balanced actions by the phenomenon of glucose homeostasis. During sleep/between meals/when blood glucose levels are low/during prolonged fasting, α-cells release glucagon and promote hepatic glycogenolysis. Along with this, glucagon do hepatic and renal gluconeogenesis and increase endogenous blood glucose levels. In elevated exogenous glucose levels, after a meal, insulin secretion is stimulated from β-cells and after docking to its receptor on muscle and adipose tissue, insulin enables insulin-dependent uptake of glucose into tissues and lowers blood glucose levels by removing the exogenous glucose from the blood stream (**Figure 2**). Moreover insulin enhances glycogenesis, lipogenesis and incorporation of amino acids into proteins; thus it performs its anabolic action as compared to glucagon which is catabolic. Along with pancreas, other organs also regulate blood glucose levels (**Figure 3**).

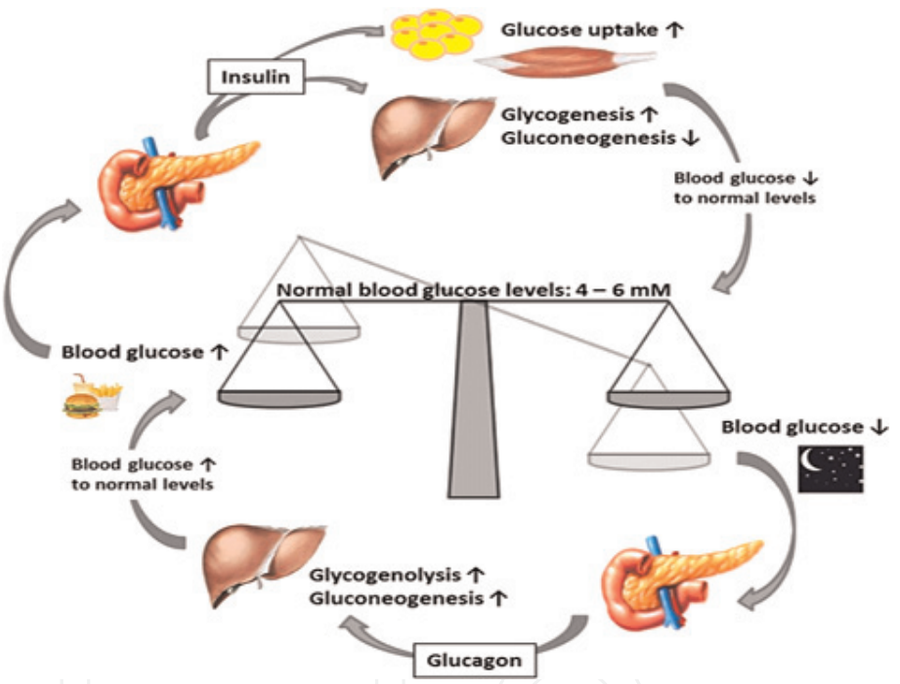
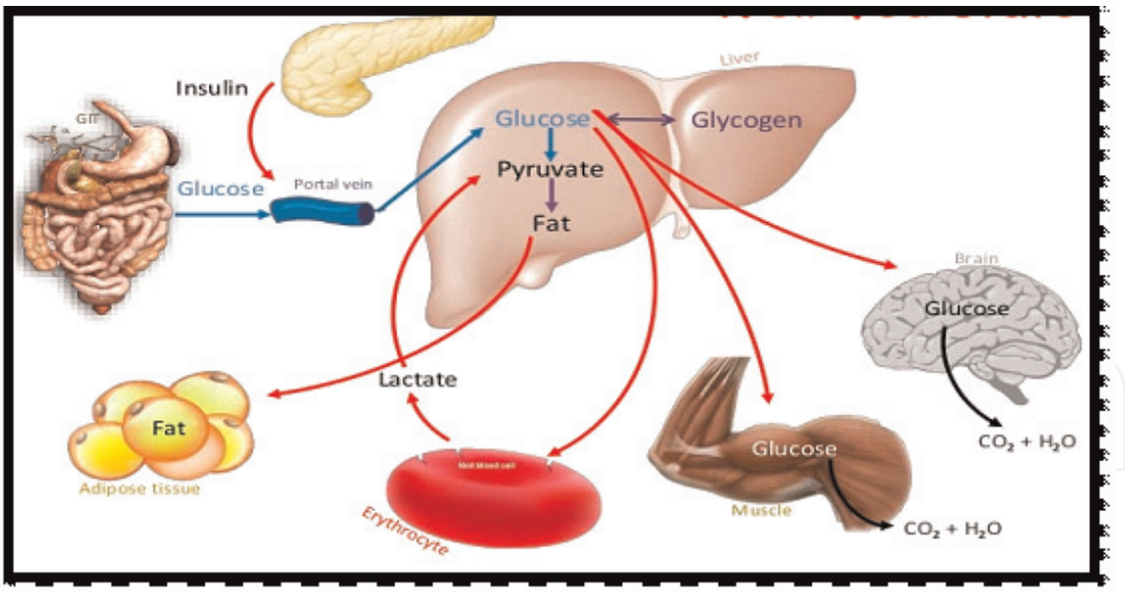


Figure 2.
Maintenance of blood glucose levels by glucagon and insulin.

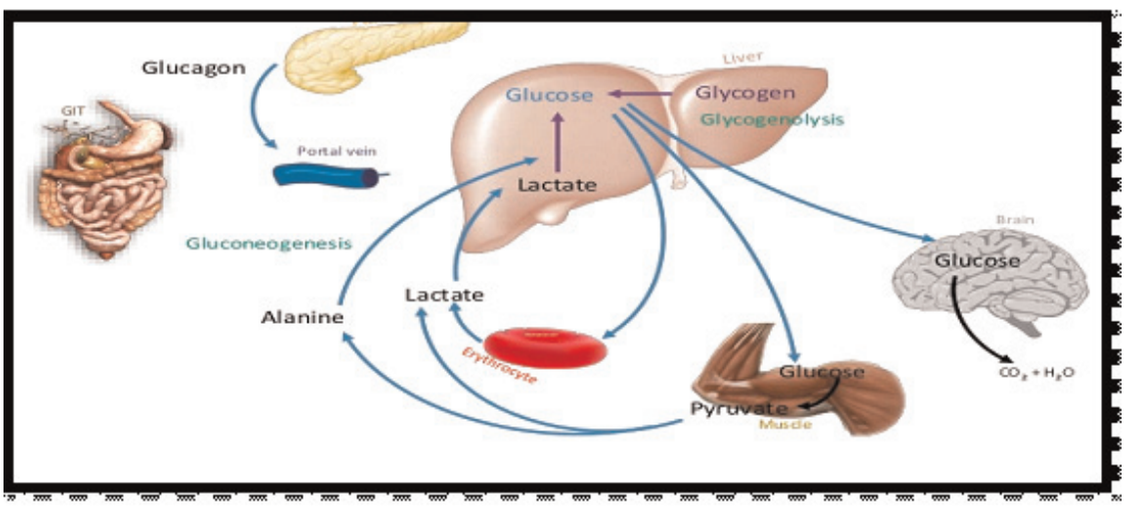
4. Genes, molecular and cellular targets to regulate blood glucose levels in normal and abnormal conditions

4.1 Genes to regulate blood glucose levels

Genetics is identifying a whole new set of genes, proteins and pathways that are related to diabetes and blood sugar control. Till now, scientist have identified a genetic disorder in MafA (it controls the production of insulin in β-cells). Surprisingly, this genetic defect was present in an unrelated family along with diabetic and insulinoma family members. The link of this gene with a defect was detected for the first time and a stable resultant mutant protein was found with a longer life in the cell, and found to be significantly more abundant in β-cells than its normal version [2].



(a)



(b)

Figure 3.
Maintenance of blood glucose levels by different organs (a) during well fed state (b) during post-prandial state.

Gene on chromosome-2 {encodes glucose-6-phosphatase catalytic 2 (G6PC2)} is linked with fasting glucose levels and is primarily expressed in pancreatic β-cells to convert glucose-6-phosphate back to glucose. Its genetic variation may be responsible for reduction in insulin secretion that increases glucose concentration. Chronically elevated levels of glucose may be a precursor for type 2 diabetes [3].

13 new genetic variants has been discovered by an international research consortium and these variants can manipulate blood glucose regulation, insulin resistance and function of insulin-secreting β-cells in European descent populations, in which 05 of the following newly discovered variants raised the risk of developing type 2 diabetes:

i. SNPs in the region of ADCY5 which influence fasting and postprandial glucose levels.

ii. FADS1 which is linked with fasting glucose as well as lipid traits.

iii. Only one variant, near IGF1 which is associated with insulin resistance

iv. β-cell impairment, which may play a larger role in type 2 diabetes than previously recognized

v. Environment which may contribute to insulin resistance more than it does to insulin secretion.

By using high-density microarray analysis, more than 31,000 genes, linked with pancreas, have been discovered and main aim was to find which gen(s) were most sensitive to glucose and fatty acids particularly from the products of high fat and sugar diets. It was found that TNFR5 gene had maximum compassion to glucose and fatty acids and due to high levels of fat and sugar, beta cells are destroyed due to its over expression. These findings suggested that people with type-II diabetes, primarily with poor blood glucose management/who have not been diagnosed, are more likely to over express this gene that leads to β cell damage. But blocking of TNFR5 in beta-cells, especially when glucose and fatty acids consumption is high, halted their obliteration which shows that reticence of TNFR5 activity could be a promising treatment strategy against type 2 diabetes [4].

To identify genetic variants responsible for blood sugar control, a genome-wide association study was done to find SNPs which could be correlated with Fasting Plasma Glucose levels. It was found that most strongly associated SNP was rs560887 in initial sampling of 650 non-obese French people. Same SNP was correlated with FPG levels in a secondary sample of 3400 same people, approximately 5000 Finns and a group of 860 obese French children. When results of all studied samples were combined, researchers found that each copy of T version of rs560887 leads to a 0.06 mmol/L reduction in FPG while rs560887 did not correlate with insulin levels or BMI of subjects. Moreover even after a 9 year follow-up period in French samples, this SNP also could not correlate with the risk of type 2 diabetes. Moreover two other SNPs; rs1260326 and rs1799884 (previously found to be associated with FPG) were also found to be significantly associated with FPG levels in same study and it was concluded that genes affected by these SNPs affect the threshold level of glucose in the bloodstream and triggered secretion of insulin by pancreas. When threshold will be higher, level of blood glucose increase even before insulin starts to regulate it [5].

4.2 Molecular pathway for blood glucose regulation

4.2.1 Glucagon and GLP-1 receptors

These are class B-GPCRs which are important targets for drugs of type 2 diabetes, obesity and blood glucose regulation problems. Structures of several class A-GPCRs have been solved, but class B receptors have not been well studied because of technical challenges. Their structures were identified and reported by four international research teams; NIDDK, NIGMS, FDA and NIDA. Structure of Glucagon receptor helps to understand how different domains cooperate in modulating the receptor function at molecular level. GLP-1 receptor, identified by cryo-electron microscopy, examined structure of receptor in complex with GLP-1 and its coupled G-protein while detailed structure of GLP-1 receptor, when bound by small molecules (that affect receptor's activity) has also been given and it is difficult to expect the importance of GPCRs which are targeted by about half of all drugs. Structural information about these receptors is crucial for further drug discovery efforts [6].

Control of blood glucose depends heavily on G-protein-coupled receptors (GPCRs) which can span cell membranes to communicate signals from the outside to inside of cell and starts a cascade of reactions in cell when once activated by binding of a substance which had made these receptors an important target for drug development. When blood glucose drops after an overnight fast, pancreas releases glucagon which binds a GPCR, glucagon receptor, on liver and muscle cells and stimulates cells to release glucose in blood. Moreover glucagon-like peptide-1 (GLP-1) hormone works by binding to another GPCR, GLP-1 receptor, on pancreatic cells. After a meal, intestine produces GLP-1, which leads to the production of insulin from pancreas to stimulate cells to pick glucose from blood [7].

4.2.2 Heterocyclic scaffolds

For many years, heterocyclic scaffolds were the basis of anti-diabetic chemotherapies as bioactive scaffolds and have been evaluated for their biological response as inhibitors against their respective anti-diabetic molecular targets over past 5 years (2012–2017). Results revealed a diverse target sets of these scaffolds including protein tyrosine phosphatase 1 B (PTP1B), dipeptidyl peptidase-4 (DPP-4), free fatty acid receptors 1 (FFAR1), G protein-coupled receptors (GPCR), peroxisome proliferator activated receptor-γ (PPARγ), sodium glucose co-transporter-2 (SGLT2), α-glucosidase, aldose reductase, glycogen phosphorylase (GP), fructose-1,6-bisphosphatase (FBPase), glucagon receptor (GCGr) and phosphoenolpyruvate carboxykinase (PEPCK) [8].

4.2.3 Incretin and adipokines

In addition to other several even newer therapies in development, Incretin-based therapies, like dipeptidyl peptidase- 4 (DPP- 4) inhibitor and glucagon like peptide-1 (GLP-1) analogues/mimetic offer a new therapeutic means for the treatment of T2DM. Moreover a great attention has been focused by many researchers on a number of potential molecular targets in adipocytes e.g. adipokines [8].

4.3 Insulin secretion signaling pathway

4.3.1 Molecular pathways for the insulin secretion

In β-cells, main stimulus for insulin release increases blood glucose levels after a meal. This blood glucose is taken up by facilitative glucose transporter GLUT2 (SLC2A2) on the surface of β-cells. Once inside the cell, glucose undergoes glycolysis and an amplified ATP/ADP ratio and this distorted ratio leads to close ATP-sensitive K^+-channels (K_{ATP}-channels). While in non-stimulated circumstances, these channels open to ensure the maintenance of resting potential by transporting K^+-ions down their concentration gradient out of the cell. Upon closure, succeeding decrease in potency of externally moved K^+-current elicits depolarization of membrane, followed by opening of voltage-dependent Ca^+-channels (VDCCs). Increase in intracellular Ca^+ concentrations ultimately triggers fusion of insulin-containing granules with membrane and succeeding release of their content. Whole secretory process is biphasic and 1st phase lasts for around 5 minutes after the glucose stimulus with the release of majority of insulin while in 2nd phase, which is somewhat slower, the remaining insulin is released. This insulin is stored in large dense-core vesicles which are recruited near plasma membrane immediately after stimulation so that it should be readily available. Key molecules that mediate the fusion of the insulin-containing large dense-core vesicles belong to the superfamily of the

soluble *N*-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor proteins (SNAREs).which are:

i. Synaptosomal-associated protein of 25kDa (SNAP-25)

ii. Syntaxin-1 and synaptobrevin 2 (or vesicle-associated membrane protein VAMP2)

Sec1/Munc18-like (SM) proteins, glucose vesicles form SNARE complex. To initiate fusion, synaptobrevin 2, a *vesicle (v-)* SNARE fuses with the *target (t-)* SNAREs syntaxin-1 and SNAP-25, which are located in the target cell membrane (**Figure 4**) [9].

Numerous SNARE isoforms [syntaxin-1, −3 and −4, SNAP-25 and -23, synaptobrevins 2 and 3 (VAMP2 and 3)] are involved in glucose-stimulated insulin secretion whereas VAMP 8 (a non-essential SNARE protein for glucose-stimulated insulin secretion) has its role to regulate glucagon-like peptide-1-potentiated insulin secretion. In addition to SNARE and SM proteins, a calcium sensor is required to initiate membrane fusion. Synaptotagmins (highly expressed in neurons and endocrine cells) participated in Ca^{2+}-dependent exocytosis processes. Seventeen synaptotagmins (Syts 1–17) have been identified while only eight (Syt-1, −2, −3, −5, −6, −7, −9 and −10) are able to bind Ca^{2+} and form a complex with the SNAREs to smooth the progress of and activate vesicle-membrane fusion process. Only Syt-3, −5, −7, −8 and −9 are concerned with insulin exocytosis [10].

4.3.2 Mechanism of insulin action

Several proteins are disturbed in the insulin signaling pathways in different conditions of insulin resistance, particularly obesity, type-II diabetes mellitus, metabolic syndrome, cardiovascular diseases, inflammatory disorders, and cancer [11].

4.3.2.1 Insulin receptor

It is tetramer protein, composed of 02 extracellular α- subunits and two trans membrane β-subunits. α-subunits have a binding site to insulin while the β-subunits contain an intrinsic tyrosine kinase activity towards intracellular side. Insulin

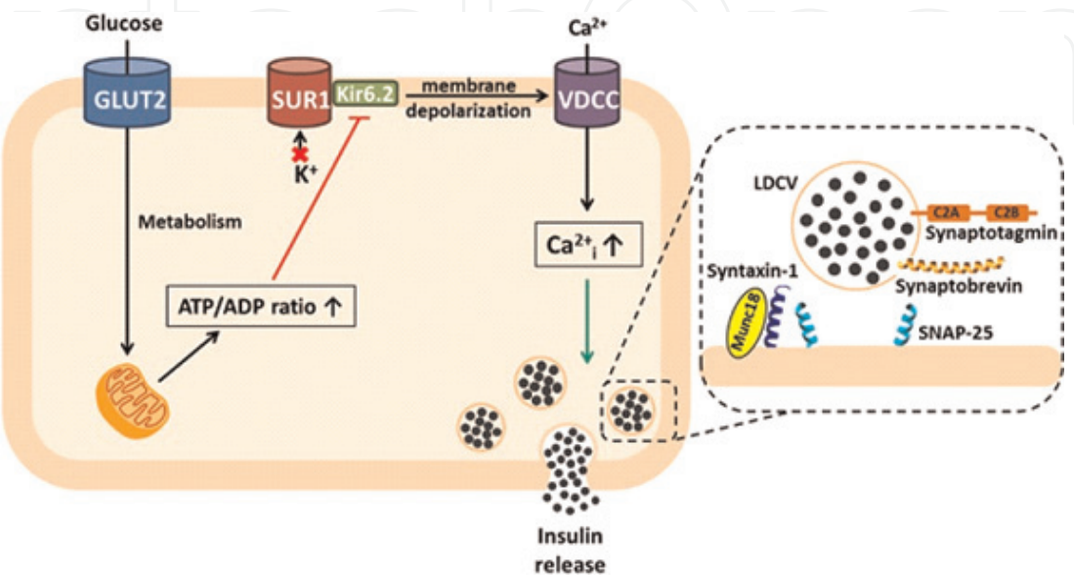


Figure 4.
Glucose-stimulated insulin release from a pancreatic β-cell.

binding to α-subunit leads to conformational change and activation of β-subunit which results in tyrosyl autophosphorylation of the insulin receptor. After being activated and phosphorylated, several major and better characterized insulin signaling intracellular docking proteins {Src homology collagen (SHC), associated protein substrate (APS) and insulin receptor substrates- 1 & 2 (IRS-1 and IRS-2)} binds to insulin receptor for tyrosyl phosphorylation. All these proteins activate glucose uptake and metabolism, protein synthesis, gene expression, cell survival, growth, development, and differentiation. IRS proteins are phosphorylated on various tyrosine residues of the C-terminal region and generate specific sites for binding of proteins containing Src homoly-2 (SH2) domains [phosphatidylinositol-3 kinase (PI-3 K), Nck, and Grb-2.

4.3.2.2 Pi-3 K

It is composed by a catalytic subunit (p110) and a regulatory subunit (p85) and mediate metabolic effects of the insulin. Binding of p85 subunit to phosphorylated tyrosine residues of IRS proteins activate catalytic activity of p110 subunit and subsequent rise in the generation of phosphatidylinositol 3,4-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-trisphosphate (PIP3) content. Downstream proteins from PI3K pathway figure out several serine/threonine kinases e.g. phosphoinositide-dependent protein kinase-1 (PDK-1), protein kinase B (PKB/Akt), protein kinase C (PKC), p70 S6 kinase (p70S6K) and glycogen synthase kinase-3 (GSK-3). All these kinases are involved in translocation of glucose transporter-4 (GLUT-4) from intracellular vesicles to plasma membrane, glycogen and protein synthesis, antiapoptotic effects and gene expression (**Figure 4**).

4.3.2.3 Cbl

Signaling pathways which are involved in glucose uptake due to insulin induction starts with the recruitment of APS to activated insulin receptor and subsequent association and tyrosine phosphorylation of Cbl which interacts with Cbl associated protein (CAP) through an SH_3 domain and with flotillin (a constituent of lipid raft, through a sorbin domain). Complex CrkII/C3G then binds to the phosphorylated tyrosine and residues of Cbl and activate C3G activity that exchanges GDP for GTP of TC10 (a small G-protein that belongs to the Rho family). After being activated, TC10 participates in GLUT-4 translocation (**Figure 5**) [12].

4.3.2.4 Mitogen-activated protein kinase (MAPK)

This cascade starts with

1. The association of Shc to insulin receptor

2. Binding of Grb-2 to Shc or to IRS-1

3. Formation of the Grb-2/SoS (Son of Seven less) in the plasma membrane.

This complex leads to the activation of c-Ras and raf, starting the MAPK cascade. MAPK pathway is involved in insulin induced differentiation, cell growth, and development, along with some metabolic effects e.g. glycogen synthesis and GLUT-4 translocation to plasma membrane (**Figure 4**). However, this cascade is not enough or even required to this later effect [13].

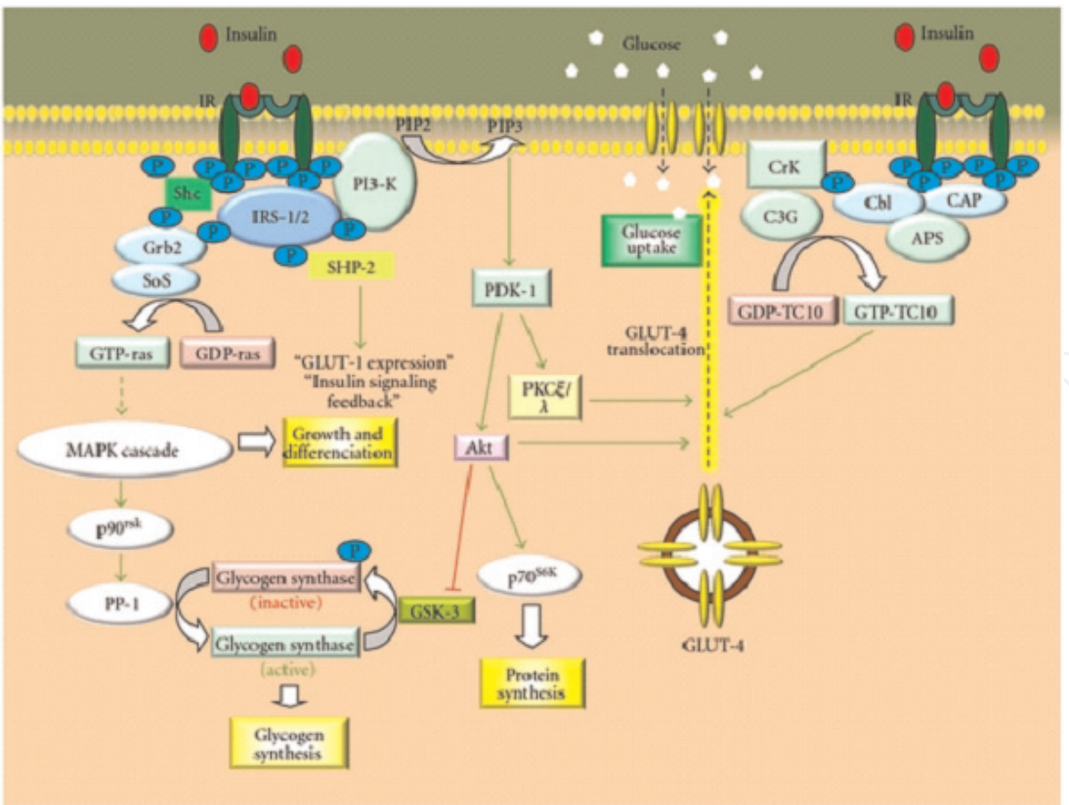


Figure 5.
Summary of the main insulin signaling pathways. GLUT-1 and -4: Glucose transporter-1 and -4; Grb-2: Growth receptor binding-2; GSK-3: Glycogen synthase kinase-3; IR: Insulin receptor; IRS-1 and -2: Insulin receptor substrate-1 and -2; MAPK: Mitogen-activated protein kinase; PDK-1: Phosphoinositide-dependent kinase-1; PIP2: Phosphatidyl-inositol diphosphate; PI3: Phosphatidyl-inositol triphosphate; P: Phosphate; PKC: Protein kinase C; PP-1: Phosphoprotein phosphatase-1; $p70^{S6K}$: Protein 70 S6 kinase; $p90^{rsk}$: Protein 90 ribosomal S6 kinase; Shc: Src homology collagen; SHP-2: Phosphatase with Src homology 2 domain; SoS: Son of Sevenless.

4.3.3 Molecular basis of insulin resistance

It occurs when insulin-sensitive tissues (skeletal muscle, adipose tissue and liver) cannot respond properly to hormones which cause several chronic diseases, particularly those which are linked to obesity (type-II diabetes mellitus, metabolic syndrome, dyslipidemias, cardiovascular diseases, cancer and neurodegenerative diseases). However precise mechanisms of insulin resistance are not fully understood. Following factor have been proposed to participate in its development;

4.3.3.1 Increased plasma-free fatty acid level

As free fatty acids are elevated in obesity and related illness, they are supposed to be responsible for insulin action impairment but still complete mechanisms are not known. More availability of long chain saturated fatty acids results leads to insulin resistance in liver, skeletal muscle and adipose tissue. Various hypotheses proposed to explain insulin resistance induced by saturated fatty acids [14] are;

i. Randle cycle

ii. Oxidative stress

iii. Modulation of gene transcription

iv. Accumulation of intracellular lipid derivatives (diacylglycerol and ceramides)

v. Mitochondrial dysfunction

vi. Inflammation

4.3.3.2 Subclinical chronic inflammation

Chronic state of inflammation in insulin responsive tissues is major contributor to insulin resistance in obesity and related diseases. However, precise mechanisms as well as mediators involved in this interaction are not completely defined yet. Intracellular redox balance is delicately synchronized process that includes multiple generating pathways and degrading systems. Physiologically, ROS contribute in essential biological responses but their accumulation causes oxidative stress condition because of their highly oxidant nature to oxidize multiple intracellular components particularly membrane phospholipids, proteins, and DNA. In insulin resistance, increased ROS production and/or decreased ROS degradation is observed that leads to an oxidative stress condition and activation of signaling pathways related to stress. Oxidative stress is also responsible for muscle disorders and contributes to insulin resistance process. Transgenic mice expressing human ubiquitin protein E3 ligase (a protein that binds and promotes degradation of superoxide dismutase-1) leads to reduced superoxide degradation and as a result increased oxidative stress in the form of atrophy and sclerosis [15].

4.3.3.3 Oxidative and nutritive stress

Activation of signaling pathways to stress is another reason of insulin resistance. Several serine/threonine kinases activated by oxidative stress pathways (JNK, PKC, GSK-3, NF-kB, and p38 MAPK) have been suggested to impair insulin signaling pathways [16].

4.3.3.4 Altered expression of several genes and mitochondrial dysfunctioning

Expression of genes involved in lipid and glucose metabolism, insulin signaling, inflammation, redox balance and mitochondrial function is modified in insulin signaling, which shows that these processes participate in the pathophysiology of insulin resistance. Disturbed mitochondrial function has been suggested to have a central role in these alterations, since this organelle participates in all these processes [17].

5. Current scenario of drugs and therapies to cure blood glucose regulation problems

5.1 Drugs

5.1.1 Drugs to manage type I and type II diabetes or its complications

Many of the drugs have a combination of effects. If a person needs two or more treatments to manage glucose levels, insulin treatment may be necessary. Possible treatments for type 1 diabetes include [18]:

1. **Metformin (Glucophage, Glumetza, others):** It is generally 1st medication for type-II diabetes and works by reducing gluconeogenesis in liver and improves body's sensitivity to insulin so that body utilizes insulin in more effective way.

2. **Sulfonylureas:** They help patients body to secrete more insulin. Its examples are glyburide (DiaBeta, Glynase), glipizide (Glucotrol) and glimepiride (Amaryl) and its possible side effects are low blood sugar and weight gain.

3. **Meglitinides**: Repaglinide (Prandin) and nateglinide (Starlix) works like sulfonylureas by stimulation of pancreas to secrete more insulin but they are faster acting with short duration of their effect in the body and have risk of causing hypoglycemia and weight gain.

4. **Thiazolidinediones:** Along with Metformin, it include rosiglitazone (Avandia) and pioglitazone (Actos). They make the body's tissues more sensitive to insulin but these drugs causes weight gain and increased risk of heart failure and anemia that's why, these medications generally aren't 1st choice treatments.

5. **DPP-4 inhibitors:** Sitagliptin (Januvia), saxagliptin (Onglyza) and linagliptin (Tradjenta) are its different forms and help to lessen blood sugar levels but tend to have very unassuming effect as they do not cause weight gain but may cause joint pain and increase pancreatitis risk.

6. **GLP-1 receptor agonists:** These are injections to sluggish digestion and lower blood sugar levels. They often cause weight loss and its possible side effects are nausea and increased risk of pancreatitis. It includes Exenatide (Byetta, Bydureon), liraglutide (Victoza) and semaglutide (Ozempic). Current research has shown that liraglutide and semaglutide may reduce risk of heart attack and stroke (in people at high risk).

7. **SGLT2 inhibitors:** They prevent kidneys from reabsorbing sugar into blood and leads to its excretion via urine. It includes canagliflozin (Invokana), dapagliflozin (Farxiga) and empagliflozin (Jardiance). They may reduce the risk of heart attack and stroke in people with a high risk of these conditions while its side effects may include vaginal yeast infections, urinary tract infections, low blood pressure and a higher risk of diabetic ketoacidosis. Only Canagliflozin in this drug class has been associated with increased risk of lower limb amputation.

8. **Insulin:** People with type-II diabetes need insulin therapy. In past, insulin therapy was used as a last option but today it's often prescribed due to its instant benefits. It's possible side effects are low blood sugar (hypoglycemia) and its different forms are:

    a. **Rapid-acting injections**: They take their effect within 5–15 minutes but last for a shorter time of 2–4 hours and include:

        i. Insulin lispro (Humalog)

        ii. Insulin aspart (NovoLog)

        iii. Insulin glulisine (Apidra)

b. **Short-acting injections**: Its effect starts between 30 minutes to 1 hour but it last for 3–8 hours e.g.

   i. Regular insulin (Humulin R and Novolin R)

c. **Intermediate-acting injections**: It is effective after 1–4 hours and last for 12–18 hours. e.g.

   i. Insulin isophane, also called NPH insulin (Humulin N and Novolin N)

d. **Long-acting injections**: They are effective after 1/2 hours and last for between 14 and 24 hours. Its different forms are:

   i. Insulin glargine (Toujeo)

   ii. Insulin detemir (Levemir)

   iii. Insulin degludec (Tresiba)

e. **Premixed injections**: These are combinations of the above types of insulin and all takes effect from 5 minutes to 1 hour and last for 10–24 hours and its different forms are:

   i. Insulin lispro protamine and insulin lispro (Humalog Mix 50/50 and Humalog Mix 75/25)

   ii. Insulin aspart protamine and insulin aspart (NovoLog Mix 50/50 and NovoLog Mix 70/30)

   iii. NPH insulin and regular insulin (Humulin 70/30 and Novolin 70/30)

f. People can breathe in **rapid-acting inhalable insulin** which produces its effects within 12–15 minutes and lasts for 2–3 hours e.g.

   i. Insulin human powder (Afrezza)

9. **Non-Inulin Injectables:**

a. **For Patients with Type-1 Diabetes:** These drugs are common for type 1 diabetic patients and its different forms are:

   i. Amylin analogs: Pramlintide (Symlin) which mimics another hormone, amylin, that plays a role in glucose regulation.

   ii. Glucagon which can reverse blood sugar levels when they fall too low as a result of insulin treatment.

b. For patients with Type-II Diabetes:

   i. **Insulin:** It can also manage high blood glucose levels in type-II diabetes but doctors typically prescribe it only when other treatments have not had the desired effect. Type-II diabetic pregnant women may also use it for the reduction of disease effects on fetus while for people with high blood glucose levels, in-spite of applying

lifestyle measures to bring them down, doctors can prescribe non-insulin drugs to lower blood glucose. These drugs are:

1. **Sulfonylureas:** They improve insulin secretion by the pancreas into blood and people use following newer medicines most often because of their less adverse effects. These are:

    a. Glimepiride (Amaryl)

    b. Glipizide (Glucotrol)

    c. Glyburide (DiaBeta, Micronase, Glynase)

    d. The older, less common sulfonylureas are:

        1. Chlorpropamide (Diabinese)

        2. Tolazamide (Tolinase)

        3. Tolbutamide (Orinase)

Today these drugs are less prescribed than in the past as they can cause hypoglycemia, leading to other health issues:

i. **Meglitinides:** They improves insulin secretion and might also improve the effectiveness of body to release insulin during meals. Its different forms are:

    1. Nateglinide (Starlix)

    2. Repaglinide (Prandin)

ii. **Biguanides:** They boost the effect of insulin, reduce the amount of glucose from liver and increase uptake of blood glucose into cells.

iii. **Metformin**: It is the only licensed biguanide in the US and is available in the form of Glucophage, Glucophage XR, Glumetza, Riomet, and Fortamet.

iv. **Thiazolidinediones**: They reduce the resistance of tissues to the effects of insulin and are associated with serious side effects so they need monitoring for potential safety issues. People with heart failure should not use these medications. They include:

    1. pioglitazone (Actos)

    2. rosiglitazone (Avandia)

    3. Alpha-glucosidase inhibitors

    4. acarbose (Precose)

    5. miglitol (Glyset)

    6. Dipeptidyl peptidase inhibitors

7. alogliptin (Nesina)
8. linagliptin (Tradjenta)
9. sitagliptin (Januvia)
10. saxagliptin (Onglyza)

v. **Sodium-glucose co-transporter 2 (SGLT2) inhibitors**: They cause body to release more glucose into the urine from the bloodstream and might also lead to a modest amount of weight loss, which can be a benefit for type-II diabetic patients. These include:

1. canagliflozin (Invokana)
2. dapagliflozin (Farxiga)
3. empagliflozin (Jardiance)
4. ertugliflozin (Steglatro)

vi. **Incretin mimetics:** The drugs that imitate incretin hormone and stimulate insulin release after meals are:

1. exenatide (Byetta, Bydureon)
2. liraglutide (Victoza)
3. dulaglutide (Trulicity)
4. lixisenatide (Adlyxin)
5. semaglutide (Ozempic)

vii. **Oral combination drugs:** Drugs that are obtained after combination of some of previous drugs include:

1. alogliptin and metformin (Kazano)
2. alogliptin and pioglitazone (Oseni)
3. glipizide and metformin (Metaglip)
4. glyburide and metformin (Glucovance)
5. linagliptin and metformin (Jentadueto)
6. pioglitazone and glimepiride (Duetact)
7. pioglitazone and metformin (Actoplus MET, Actoplus MET XR)
8. repaglinide and metformin (PrandiMet)
9. rosiglitazone and glimepiride (Avandaryl)
10. rosiglitazone and metformin (Avandamet)

11. saxagliptin and metformin (Kombiglyze XR)

12. sitagliptin and metformin (Janumet and Janumet XR)

viii. **Alternatives**: U.S. Food and Drug Administration has permitted ergot alkaloid, bromocriptine (Cycloset) to treat type-II diabetes. Doctors do not often propose/set down this medication. Moreover people use bile acid sequestrants to manage cholesterol levels which can also help to maintain steady blood sugar levels. Along with these, only colesevelam (Welchol) is approved for type-II diabetes.

5.1.2 Drugs that may help to prevent the complications of diabetes.

5.1.2.1 ACE inhibitors or angiotensin-II receptor blockers

They are used to treat high blood pressure to prevent or manage kidney complications of diabetes.

5.1.2.2 Statins and aspirin

People can manage cardiovascular risks of diabetes (like heart disease and stroke) by taking them to lower cholesterol levels at a dozen of once per day on doctors recommendation.

5.1.2.3 Drug for weight loss

It is key part of diabetes management and prevention and doctors might suggest medicines to cure it without effective lifestyle measures [19]. These drugs are

i. **Lorcaserin (Belviq)**: It enhances the feeling of being packed after food and help to treat diabetic obesity.

ii. **Orlistat (Alli and Xenical):** This drug decreases absorption of fat from diet and also support weight loss.

iii. **Phentermine and topiramate (Qsymia):** It is a grouped drug and reduce appetite to treat obesity.

5.1.3 Current guidelines at each person's situation and best approach for the individual

There are many guide lines for each person's health situation and each can choose best one according to their health conditions [20] e.g.

i. For people with type 2 diabetes and atherosclerotic cardiovascular disease (CVD), 2018 guidelines recommend following drugs as part of the antihyperglycemic treatment:

   a. Sodium-glucose cotransporter 2 inhibitors (SGLT2)

   b. Glucagon-like peptide 1 receptor agonists (GLP1-RA)

ii. Type-II diabetic people with atherosclerotic CVD and heart failure or a high risk of heart failure should be prescribed with:

   a. Sodium-glucose cotransporter 2 inhibitors

iii. To treat people with type-II diabetes and chronic kidney disease, doctors urged to consider following guidelines to stop chronic kidney disease, CVD or both, from getting worse.:

a. Sodium-glucose co transporter 2 inhibitor

b. Glucagon-like peptide 1 receptor agonist

5.2 Therapies

When medicines and lifestyle changes are not enough to manage diabetes, a less common treatment can become an option. Other treatments include different surgical procedures for treating type-I or type-II diabetes [21–25] which are as follows:

5.2.1. Bariatric surgery

It is also called weight-loss surgery or metabolic surgery and it help obese and type-II diabetic patients to lose a large amount of weight and regain normal blood glucose levels. Even some people with diabetes may no longer need their diabetes medicine after it. Efficacy of this surgery can be checked by the variations in blood glucose level, type of weight-loss surgery and the amount of lost weight by the patients. Moreover it can also be monitored by the time occurrence of diabetes and on duration of usage of insulin. Current research suggested that weight-loss surgery also may help to improve blood glucose control in obese type-I diabetic people but still scientists are finding long-term results of this in type-I and II diabetic patients [21].

5.2.2 Artificial pancreas

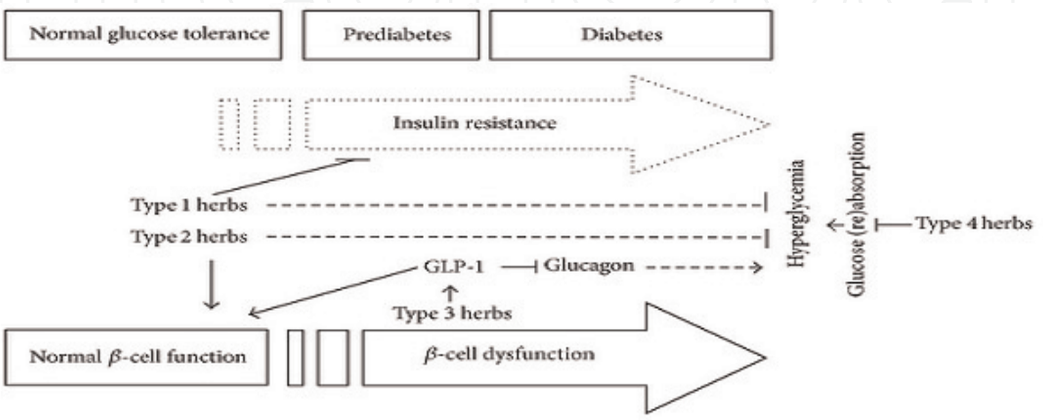
NIDDK has leading role to develop artificial pancreas technology. Artificial pancreas replaces manual blood glucose levels by the shots or pumping of insulin. Single system monitors blood glucose levels throughout the patient's life and provide insulin or a combination of insulin and glucagon routinely. The system can also be monitored remotely by parents or by medical staff. In 2016, FDA approved a type of artificial pancreas system, called a hybrid closed-loop system which tested blood glucose level after every 5 minutes throughout the day and night and automatically provided right amount of insulin to body. But when person still needed manual adjustment of insulin amount, pump delivered it at meal times. But artificial pancreas make patient free from some of daily tasks which are needed to keep blood glucose level steady or help to sleep through the night without need of wake and test blood glucose or to take medicine. Hybrid closed loop system was available in the U. S. in 2017. NIDDK has funded several important projects on different types of artificial pancreas devices for the better help of Type- I diabetic people for proper management of disease. These devices may also help type-II diabetic and gestational diabetic people to cure their disease [22, 23].

5.2.3 Pancreatic islet transplantation

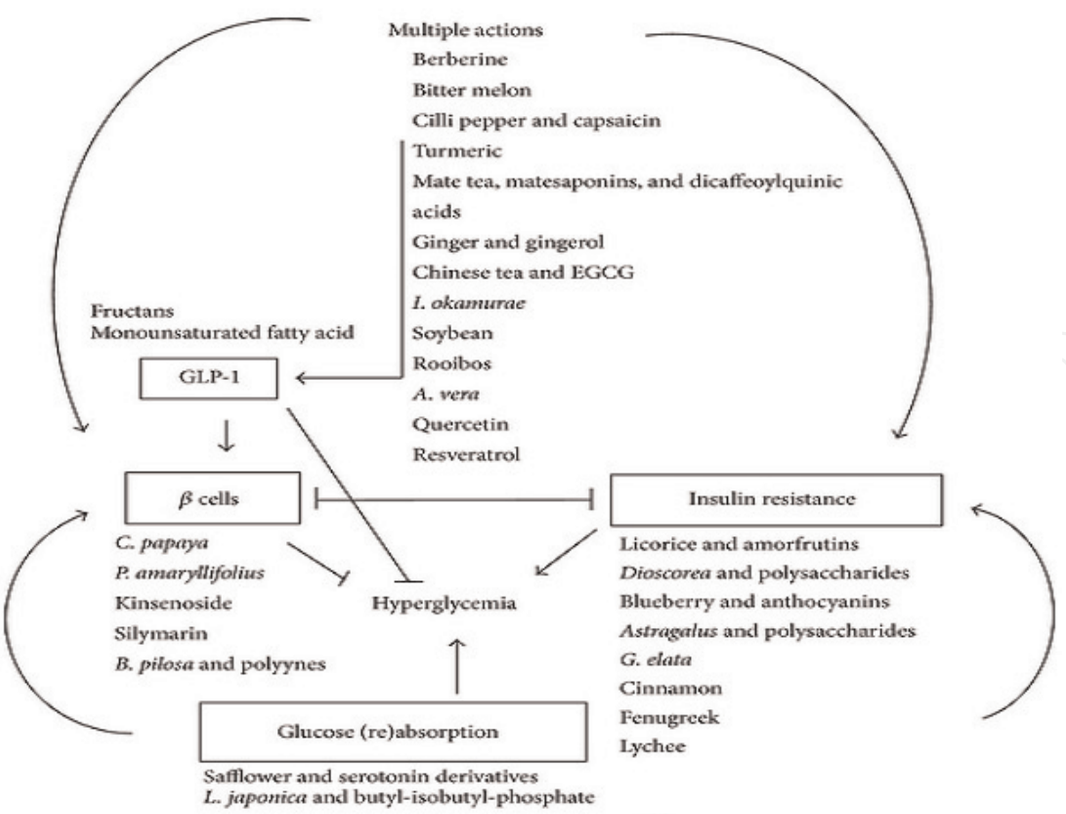
This is an experimental treatment for poorly controlled type-I diabetes as in this condition immune system attacks islet cells. Pancreatic islet transplant replace shattered islets with new ones to make and release insulin. In this process, islets are donated from the pancreas of donor of pancreas and are transferred to a type 1 diabetic patient. As researchers are still doing work on pancreatic islet transplantation, so procedure is only accessible to volunteers of research studies [24, 25].

6. New approaches to drug development and therapies, with a particular focus on drug development by green synthesis to cure blood glucose regulation problems

Bioactive molecules from Natural products have been proved to improve insulin resistance and its associated complications by suppressing inflammatory signaling pathways [26]. Medicinal plants cannot be obsolete and still play a prominent role in human health care. Among natural sources, over 1200 plants have been claimed as antidiabetic remedies. While over 400 plants along with its 700 recipes and compounds have been scientifically evaluated for type-II diabetes. Metformin was developed on the basis of

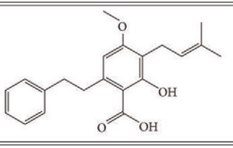
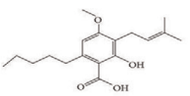
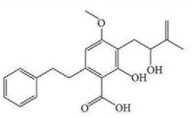
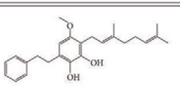
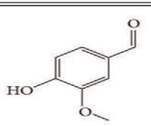
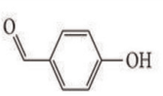
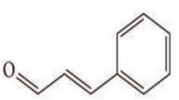
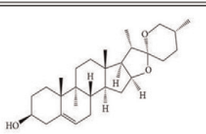
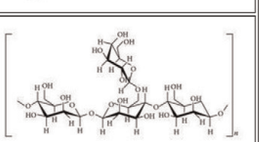
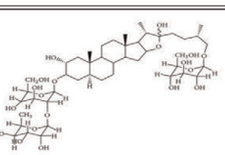
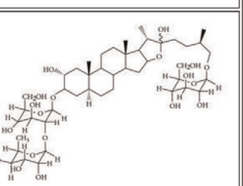
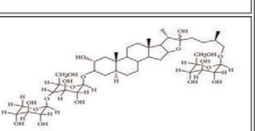
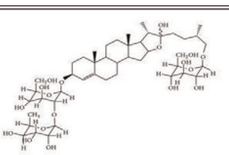


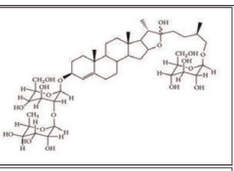
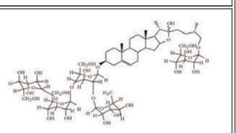
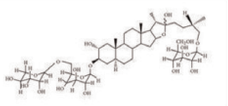
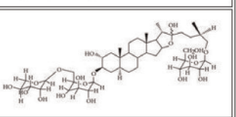
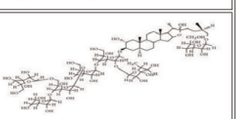
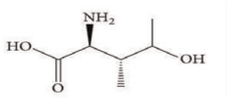
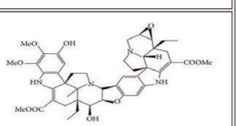
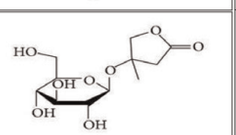
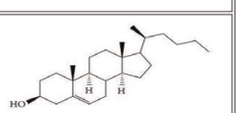
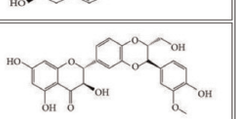
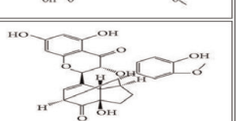
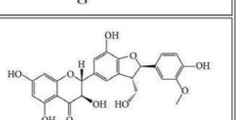
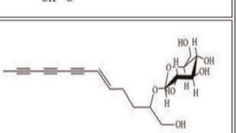
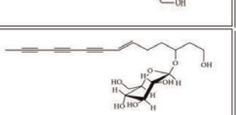
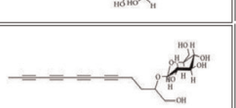
(a)

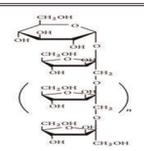
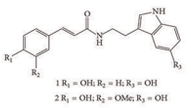
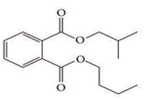
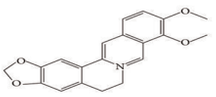
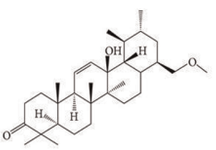
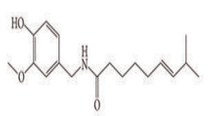
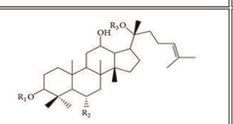
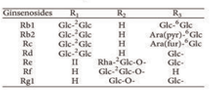
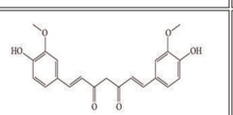
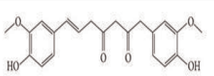
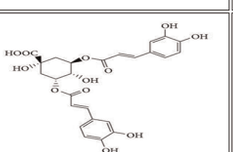
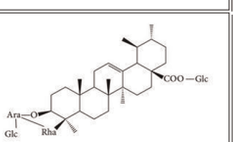
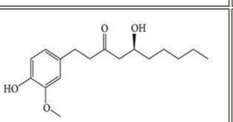
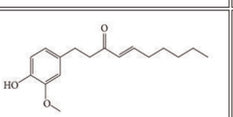


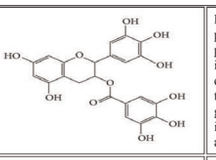
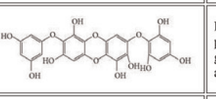
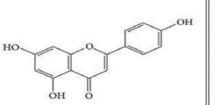
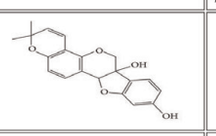
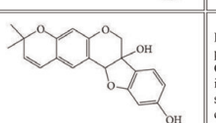
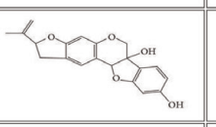
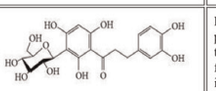
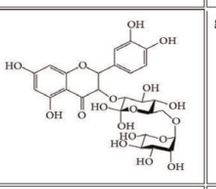
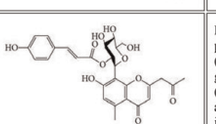
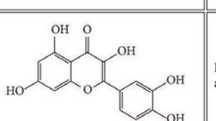
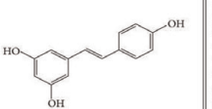
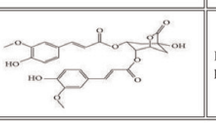
(b)

Figure 6.
Mechanisms underlying herbal therapies using antidiabetic plants and phytocompounds. (a) Different types of medicinal herbs can be classified based on their modes of action such as insulin resistance (type 1 herbs), -cell function (type 2 herbs), and GLP-1 (type 3 herbs) and glucose (re) absorption (type 4 herbs), (b) The selected.

Herb	Compound name	Chemical structure	Antidiabetic mechanism (s)
G. uralensis	Amorfrutin 1		Regulate insulin resistance
	Amorfrutin 2		
	Amorfrutin 3		
	Amorfrutin 4		
D. rhizome	Dioscorea polysaccharides	N.A.	
V. spp.	Phenolics and Anthocyanins	N.A.	
A. membranaceus	Astragalus polysaccharides	N.A.	
G. elata	Vanillin		Reduces insulin resistance
	4-hydroxybenzaldehyde		
C. verum *C. zeylanicum* *C. aromaticum*	Cinnamaldehyde		Regulate insulin resistance
T. foenum-graecum	Diosgenin		Reduces insulin resistance.
	Galactomannan		
	Trigoneoside Xa		
	Trigoneoside Xb		
	Trigoneoside XIb		
	Trigoneoside XIIa		

	Trigoneoside XIIb		
	Trigoneoside XIIIa		
	Trigoneoside Ia		
	Trigoneoside Ib		
	Trigoneoside Va		
	4-hydroxyisoleucine		
L. chinensis	Oligonol (mixture of compounds)	N.A.	Regulate insulin resistance
C. papaya P. amaryllifolius	Flavonoids, alkaloids, saponin, and tannins	N.A.	Regulate β-cell function
T. divaricate E. microphylla	Conophylline		
A. roxburghii	Kinsenoside		
N. stellata	Nymphayol		
S. marianum	Silybin		
	Silydianin		
	Silychristin		
B. pilosa	3-β-D-glucopyranosyl-1-hydroxy-6(E)-tetradecene-8,10,12-triyne		
	2-β-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne		
	2-β-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (cytopiloyne)		
G. sylvestre	No reported active compounds	N.A.	

Dietary fibers from the roots of *A. tequilana,* Dasylirion spp. and so forth	Inulin/Raftilose		Regulate GLP-1 homeostasis
Olive oil	Monounsaturated fatty acids	N.A.	
C. tinctorius	Serotonin derivatives	 1 R_1 = OH; R_2 = H; R_3 = OH 2 R_1 = OH; R_2 = OMe; R_3 = OH	Regulate glucose absorption in the guts
L. japonica	Butyl-isobutyl-phthalate		
B. vulgaris	Berberine		Regulate two or more pathways (lower hyperglycemia, increase insulin resistance, pancreatic β-cell regeneration, and decrease lipid peroxidation)
M. charantia	Momordicin		Regulate two or more pathways (lower blood glucose due to their insulin-like chemical structures)
Capsicum plan ts	Capsaicin		Regulate two or more pathways (regulation of insulin resistance and probably β cells)
P. ginseng	Ginsenoside Rb1 Ginsenoside Rb2 Ginsenoside Rc Ginsenoside Rd Ginsenoside Re Ginsenoside Rf Ginsenoside Rg1	 	Regulate two or more pathways (regulate β-cell function, improvement of insulin resistance)
C. longa	Curcumin		Regulate two or more pathways (regulation of insulin resistance and β-cell function)
	Turmerin		
I. paraguariensis	3,5-O-dicaffeoylquinic acid		Regulate two or more pathways (augmentation of GLP-1 production)
	Matesaponin 2		
Z. officinale	Gingerol		Regulate two or more pathways (islet cell protection and increased insulin receptor signaling)
	Shogaol		Unclear but can elevate glucose uptake in response to insulin in muscles and adipose cells

C. sinensis	Epigallocatechin 3-gallate (EGCG)		Regulate two or more pathways (islet protection, increase in insulin secretion, decrease in insulin tolerance, decrease in gluconeogenesis and insulin-mimetic action)
I. okamurae	Diphlorethohydroxycarmalol		Regulate two or more pathways (α-glucosidase and α-amylase inhibitor)
G. max	Genistein		Regulate two or more pathways (preserves islet mass, activates protein kinase A (PKA) and extracellular-signal-regulated kinases (ERK) 1/2, activates AMPK, and reduces insulin sensitivity)
	Glyceollin I		
	Glyceollin II		Regulate two or more pathways (enhance GLP-1 secretion, improve insulin secretion, regulate β-cell function)
	Glyceollin III		
A. linearis	Aspalathin		Regulate two or more pathways (insulin tolerance, β-cell function, and inhibition of α-glucosidase)
	Rutin (quercetin-3-O-rutinoside)		
A. vera	Aloeresin A		Regulate two or more pathways (suppression of α-glucosidase activity (gut glucose absorption) and insulin resistance)
Commonly found in plants, vegetables, and fruits	Quercetin		Regulate glucose absorption in guts.
Commonly found in plants and fruits	Resveratrol		Regulate two or more pathways (activates AMPK and downstream molecules, prevents cell death of pancreatic β cells, and activates SIRT1)
Coffee	Quinides (e.g. (1R,3R,4S,5R)-3,4-diferuloyl-1,5-quinide)*		Regulate two or more pathways

N.A.: not applicable

Quinides are derived from chlorogenic acid during roasting

Table 1.
Active compounds and biological actions of antidiabetic herbs.

biguanide compound from an antidiabetic herb, *French lilac* and is now its a first-line drug against type-II diabetes. Medicinal plants also contains a diverse bioactive compounds and can have multiple actions on insulin action, insulin production, or both. With a focus on scientific studies of selected glucose-lowering herbs, phyto compounds

and their ability to target insulin resistance, cell function, incretin related pathways and glucose (re)absorption (**Figure 6a** and **b**), multiple studies have been done.

While more than 400 plants and compounds have shown *In-vitro* and/or *In-vivo* antidiabetic activities. Instead of listing each extract/compound, here, selected chemicals from plants and/or their extracts with the ability to control blood glucose levels as well as to modulate mechanisms involved in insulin resistance or cell function or incretin-related pathways or glucose (re)absorption can be tabulated (**Table 1**) along with chemical structure, antidiabetic activity and action in cells/animal models and the results of administration of the plant extracts and compounds to diabetic patients [27].

7. Conclusions

All hormones for the regulation of blood glucose levels along with their source organ up to the level of cell have been discussed in first section of chapter. Then different Pathways involved in regulating blood glucose levels in normal and abnormal conditions has been explained. Genes, Molecular and cellular targets to regulate blood glucose levels in normal and abnormal conditions has been discussed with particular focus on molecular basis of insulin signaling pathways and this pathway has been linked with Mechanism of Insulin Action and Molecular Basis of Insulin Resistance which is may be due to fatty acids, inflammation, stress and altered expression of several genes. Current scenario of Drugs and therapies to cure blood glucose regulation problems for the management of type 1 and type 2 diabetes has been explained. At the end New approaches to drug development and therapies by green synthesis to have been mentioned.

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Conflict of interest

All authors declare that they do not have any conflict of interest with any company or organization or person.

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Abbreviations

MafA	musculoaponeurotic Fibrosarcoma Oncogene Family, A
MafB	musculoaponeurotic Fibrosarcoma Oncogene Family, B
SNPs	single Nucleotide Polymorphism
ADCY5	adenylate cyclase 5
FADS1	fatty acid desaturase 1

IGF1	insulin-Like Growth Factor 1
B-GPCRs	class B G protein-coupled receptors
class A-GPCRs	class A G protein-coupled receptors
Cbl	cannabinoid 1
GDP	guanosine diphosphate,
GTP	guanosine diphosphate,
Shc	Src homology and collagen protein
c-Ras	rat sarcoma
raf	rapidly Accelerated Fibrosarcoma
JNK	c-Jun N-terminal kinase
PKC	protein kinase C
GSK-3	glycogen synthase kinase-3
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
p38 MAPK	p38 mitogen-activated protein kinases
ACE inhibitors	acetylcholine Esterase Inhibitors
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
FDA	Food and Drug Administration
NIGMS	National Institute of General Medical Sciences
NIDA	National Institute on Drug Abuse

Author details

Asma Ahmed[1*] and Noman Khalique[2]

1 Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore, Lahore, Pakistan

2 Department of Zoology, University of the Punjab, Lahore, Pakistan

*Address all correspondence to: asma.ahmed@imbb.uol.edu.pk; asma.ahmad.aridian@gmail.com

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