

Plants Secondary Metabolites

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Plant secondary metabolites were reported to inhibit carbohydrate metabolizing enzymes, possess kinase activating capacity, thereby affecting all the metabolic pathways of carbohydrate, lipid and protein, and can intervene in the insulin-signaling pathway, inflammatory response, and oxidative stress and restore molecular aberrations leading to insulin resistance and glucose intolerance.

Keywords: diabetes ; secondary metabolites ; alkaloids ; flavonoids ; coumarins ; insulin signal

1. Introduction

Phytomedicine is a plant-based medicine, and it is one of the subsets of complementary and alternative medicinal (CAM) therapies ^[1]. The World Health Organization (WHO) defined herbal medicine as the knowledge, skills and practices based on the views and experiences related to different cultures used in the preservation of health and the prevention, diagnosis, improvement, or treatment of illness ^{[2][3]}. Traditional herbal medicines are plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing conventionalisms ^[2].

Published research has proven that several secondary metabolites demonstrate hypoglycemic activity in vivo and in vitro, and usually, they affect multiple targets, proteins and enzymes. Alkaloids, phenols, anthocyanin, flavonoids, saponins, tannins, terpenes and coumarins were found to elicit a significant influence on diabetes ^{[4][5]}.

Phlorizin is a natural dihydrochalcone found in a number of fruitful trees, mainly the *Malus* genus. It produces renal glycosuria and blocks intestinal and renal glucose reabsorption by inhibiting the sodium-glucose symporters located there ^{[6][7]}. Recently, ertugliflozin arrived as the newest synthetic GLT-2 (glucose transporter-2) inhibitor to receive FDA approval for the treatment of diabetes ^{[8][9]}.

This review highlights the proposed secondary metabolites mechanism-based action targeting various metabolic pathways involved in glucose metabolism in humans. The summarized data from in vivo and in vitro bioassays of phytochemicals will lead future research towards developing effective antidiabetics with low toxicity.

2. Mechanisms Involved in Glucose Metabolism and Homeostasis

Starch is mainly converted to glucose by the action of α -amylase that hydrolyzes macromolecules into oligoglucans, and α -glucosidase further degrades oligoglucans into absorbable glucose molecules at the brush border of the small intestine and is then absorbed through the glucose transporters sodium-dependent glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2) ^{[10][11]}. Several phytoconstituents are known to suppress the activity of α -amylase, α -glucosidase and to inhibit intestinal absorption of glucose, inhibiting postprandial hyperglycemia and keeping the concentration of glucose in the blood constant after a meal ^{[10][12]}.

Other secondary metabolites can modulate the secretion of glucagon-like peptide-1 (GLP1), inhibiting dipeptidyl peptidase-4 (DPP4) from extending the effect of GLP1. In L-cells of the small intestine, basal serum GLP1 is released in response to nutrients loads (**Figure 1**). It promotes insulin secretion and stimulates the hypothalamus gland to induce postprandial satiety and to inhibit glucagon secretion. GLP1 has a very short half-life because it is hydrolyzed by dipeptidyl peptidase-4 (DPP4) ^{[13][14][15]}.

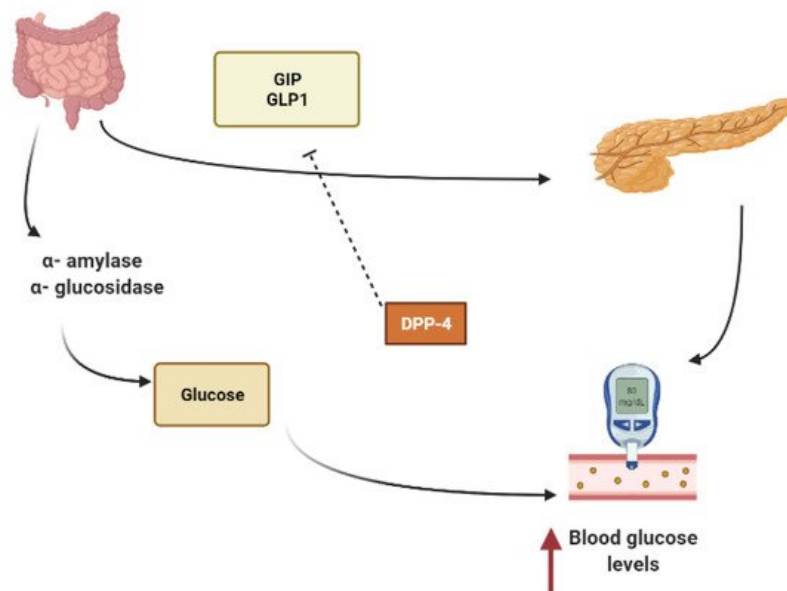


Figure 1. Carbohydrate metabolism in the gastrointestinal tract.

To maintain constant blood glucose levels, various body organs, including the pancreas, liver, intestine, adipose and muscle tissues with various hormones and neuropeptides, work together. The pancreas plays a crucial role in glucose homeostasis by secreting insulin and its opponent glucagon [16]. The increased circulating glucose is sensed by pancreatic β -cells and subsequently glucose influx into the cells via GLUT2, an insulin-independent transporter (**Figure 2**). Glucose induces insulin secretion from β -cells via the closure of ATP-gated potassium channels and activation of voltage-gated calcium channels [11][16][17][18].

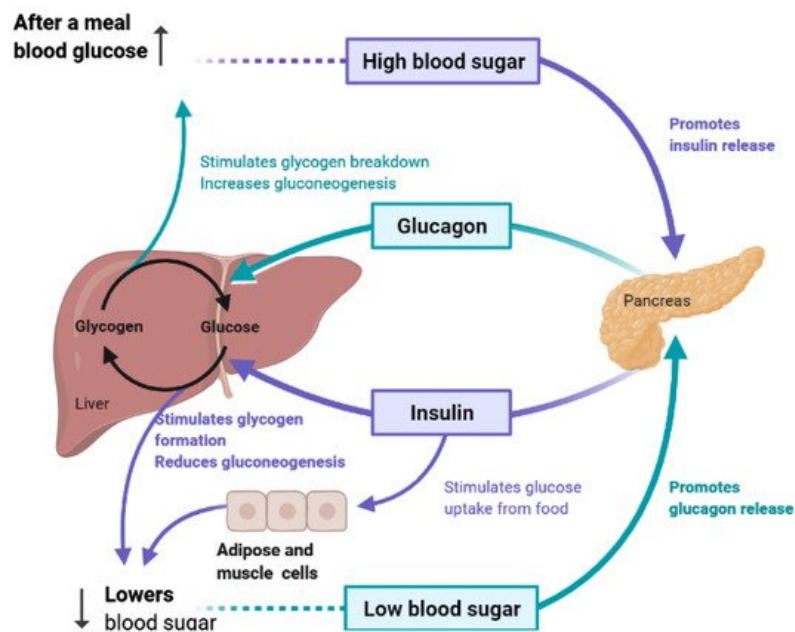


Figure 2. Carbohydrate balance.

Several medicinal plants constituents can affect insulin secretion via closing the ATP-sensitive potassium channel (KATP), acting on the Ca^{2+} channels. Others can decrease insulin degradation by inhibiting insulinase or by possessing cAMP phosphodiesterase inhibitory activity (**Figure 3**) [17].

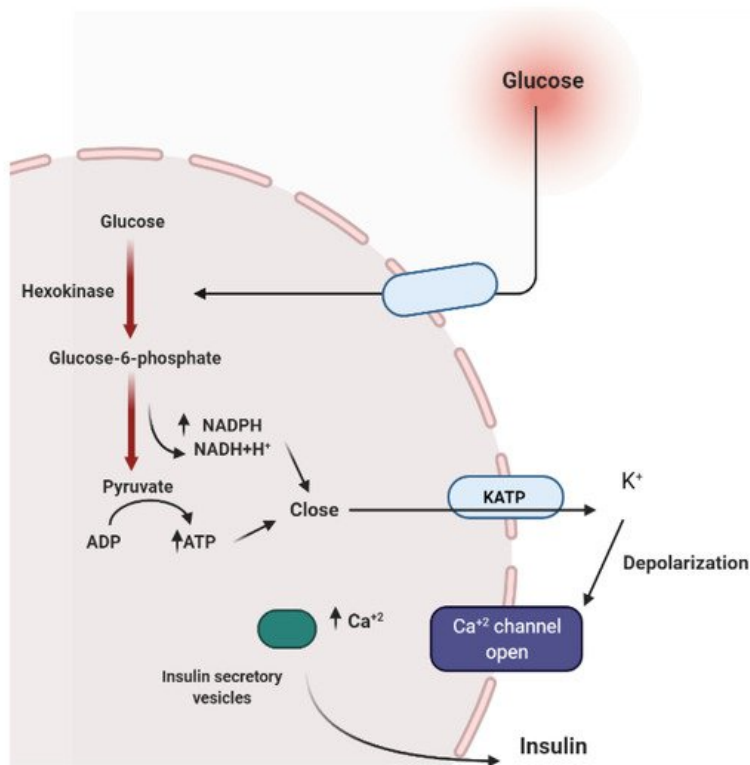


Figure 3. Mechanism of insulin exocytosis.

3. Liver and Glucose Homeostasis

The liver is the chief organ in maintaining glucose homeostasis through controlling various pathways, including glycogenesis, glycogenolysis, glycolysis and gluconeogenesis [19]. During feeding conditions, glucose is a primary fuel source across multiple fuel sources across numerous body tissues by eliciting ATP molecules during hydrolysis and the Krebs cycle. The increase in glucose uptake in hepatocytes promotes glycolysis and lipogenesis to generate triglycerides as storage forms of fuel [17][19]. Glycolysis can be regulated through the reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase (Figure 5 and Figure 6). Moreover, there are seven enzymes involved in this Krebs cycle, of which only two enzymes, succinate dehydrogenase and malate synthase, can be regulated. Several plant secondary metabolites (discussed below) can regulate and affect these enzymes except for the pyruvate kinase enzyme [17][20][21].

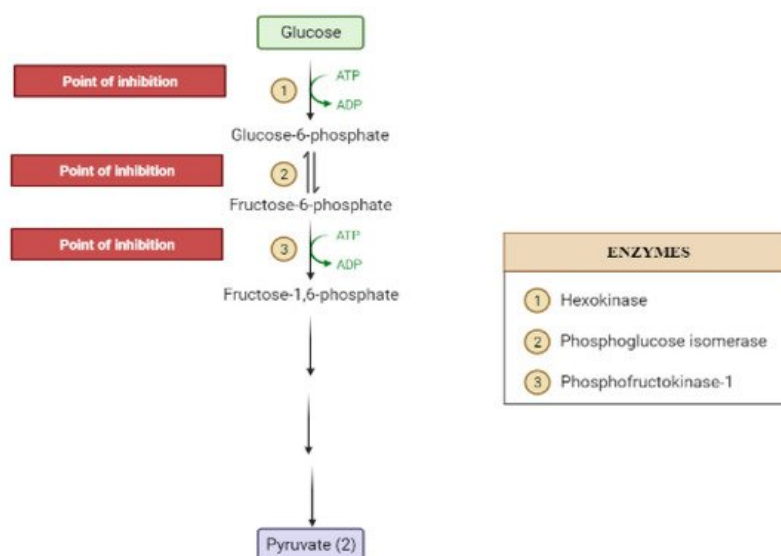


Figure 5. Glycolysis.

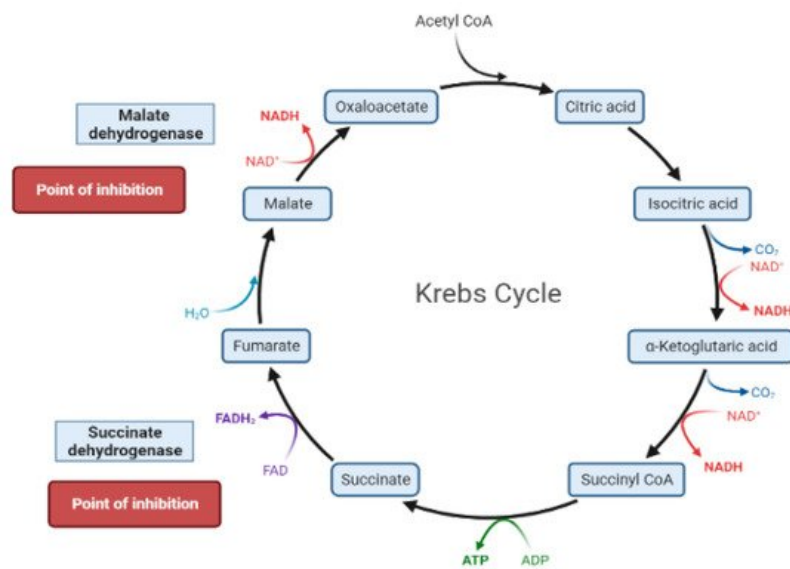


Figure 6. Krebs cycle.

During the fasting state, the liver is the leading factory for glucose production through gluconeogenesis and glycogenolysis. The main regulatory enzymes in the gluconeogenesis pathway include glucose 6-phosphatase (G6Pase), fructose 1, 6-bisphosphatase (Fbpase1), PC (pyruvate carboxylase), and phosphoenolpyruvate carboxykinase (PEPCK), all can be inhibited by plant secondary metabolites (**Figure 7**)^{[19][20]}.

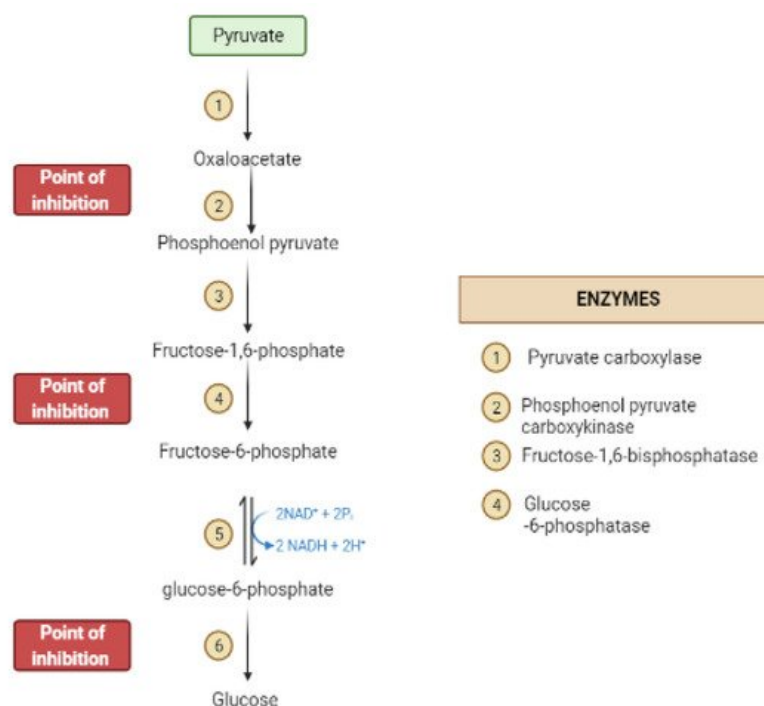


Figure 7. Gluconeogenesis.

Glycogen synthesis from unused glucose is a multistep process carried out by the enzyme glycogen synthase in the liver. Secondary metabolites can affect the process through glycogen synthase. In addition, glycogenolysis is inhibited through glycogen phosphorylase (**Figure 8**)^[17].

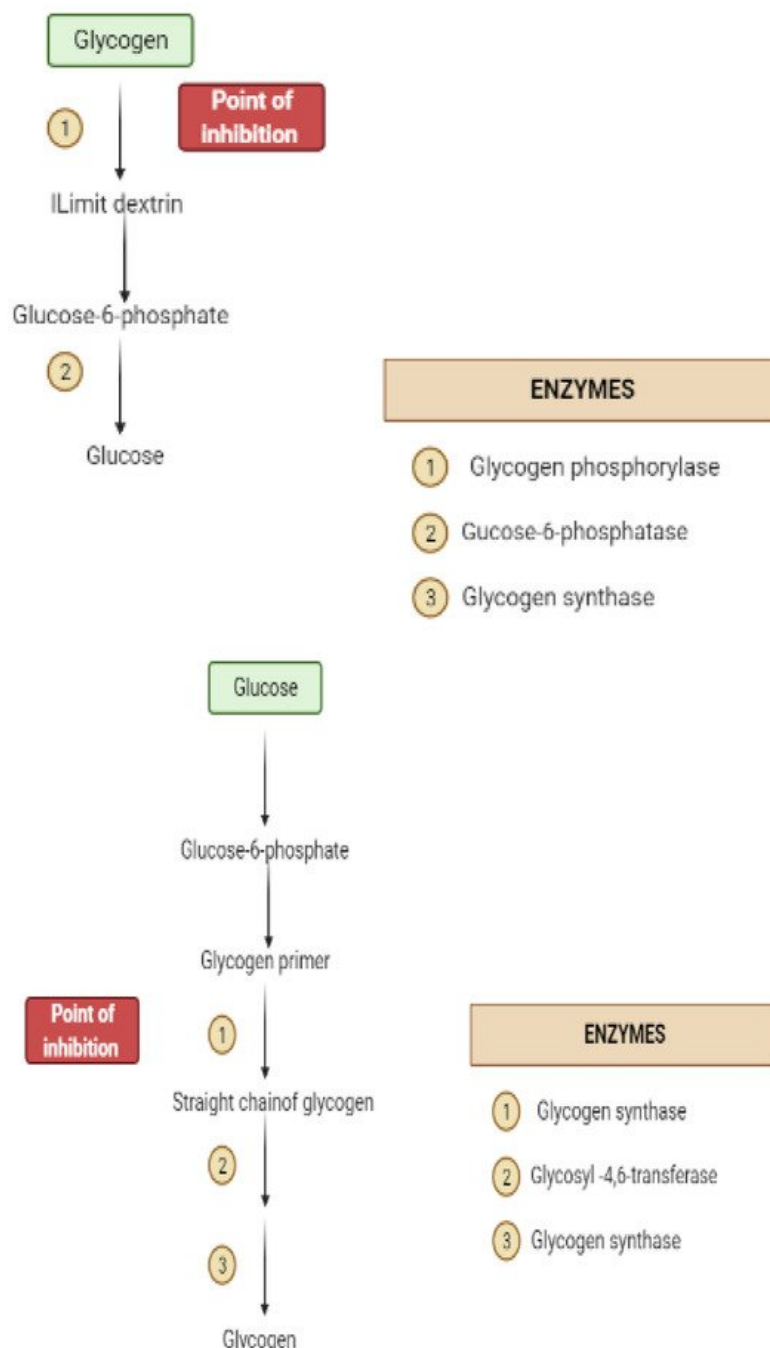


Figure 8. Glycogen metabolism, synthesis and hydrolysis.

4. Obstacles for Insulin Signal Transduction and Insulin Effects

The increase in the free fatty acids is connected to alteration in the diacylglycerol (DAG)/protein kinase C (PKC) pathway. The rise in DAG activates PKC- θ , - $\beta 2$ and - δ that phosphorylates IRS1, which interferes with insulin-stimulated phosphorylation of IRS1, thus inhibiting insulin signaling. It is believed that targeting PKC is beneficial in treating type 2 diabetes as it will address the secretory defect promoting insulin secretion [22][23].

Inflammatory mediators (such as TNF- α , IL-6) can impair insulin and promote serine phosphorylation of IRS-1 impairing insulin signaling or can cause degradation of IRS. It can reduce GLUT-4 expression, decreasing glucose entry to cells and cause inflammation-induced nitric oxide release that suppresses PI3K-Akt pathway [18]. It is well-known that inflammation is a crucial cause for diabetes type-2. Relieving inflammation by secondary metabolites can improve diabetes [24].

Oxidative stress has been linked to diabetes. It comprises insulin secretion and insulin action. It activates NF- κ B and JNK, IRS degradation, suppresses GLUT-4 expression and translocation, activates inflammatory responses [25][26]. Plant secondary metabolites can stimulate mitochondrial metabolism and/or decrease mitochondrial dysfunction through targeting sirtuin 1 activators (SIRT1) and PPAR α [26].

A dependent relationship exists between insulin and mitochondria. Insulin release depends on mitochondrial ATP production, and mitochondrial fusion depends on insulin. Mitochondria is a major source of free radicals. However, overproduction of free radicals causes mitochondrial dysfunction [26][27].

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