Journal of Nutrition and Dietetics

Extended Abstract Open Access

Future Prospects of Developing Anti Diabetic Drugs from Plants and Cvot Trails of Empagliflozin

Kulvinder Kaur

Dr Kulvinder kaur centre for human reproduction, India

Keywords

T2DM; SGLT2 Inhibitors; CVOT; Empagliflozin; Liraglutide Monoterpenes

Abstract

Hyperglycemia seen in T2DM occurs secondary to pancreatic functional impairment along with insulin resistance (IR), correlated with imbalance in glycogenolysis and gluconeogenesis rates enhanced endogenous glucose synthesis. Decrease in lipid was seen in total cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL), and triglycerides amounts with escalation of high density lipoproteins (HDL) amounts.

DM presents with low plasma HDL with high triglycerides (TG), total cholesterol (TC), and LDL amounts. Escalated LDL prevents insulin release and causes pancreatic B –cell apoptosis, although rise in HDL helps against apoptosis along with increase in pancreatic B –cell function, decreased plasma glucose and enhanced insulin. Collection of TG in liver, pancreas and muscles is associated with IR and the TC levels in adipocytes enhancement with > amts of TG's. As DM represents a complicated disease, there is requirement for agents that have multiple targets instead of single target approach by one drug. In view of this plants like herbs and spices represent a very lucrative therapy for DM since variety of protein targets might be controlled with >1 agent. In the study of Pereira., et al. almost 50% of the herbs and spices were shown to be having a good percentage that have multiple targets that are cinnamon, cumin, fennel, fenugreek, lemon balm, liquorice, oregano, lemon grass, saffron, marjoram, rosemary, sage, thyme. The main antidiabetic actions seen in earlier works were a decrease in hyperglycemia and hyperlipidemia, along with control in insulin secretion. In figure 1, actions of each herb and spices on these 3 DM hallmarks based on the protein targets of the DIA-DB webserver is observed. All herbs and spices were shown to be potential controllers of ≥12 protein targets except paprika and cardamom, whose agents were only observed as potential controllers of 5 and 9 targets, respectively. Decrease in hyperglycemia can be due to the control of the protein targets that take part in glucose metabolism. AMY2A and MGAM Inhibition delays digestion of the carbohydrates and hence reduce the postpartum blood glucose amount. FBP1 and PYGL inhibition inhibits endogenous glucose synthesis through liver via inhibition of gluconeogenesis and glycogenolysis respectively and hence decreasing blood glucose. PDK's get upregulated in DM and thus cause inhibition of pyruvate dehydrogenase kinase complex which in turn causes pyruvate → Acetyl CoA conversion, which then enters the Kreb's cycle. With inhibition of PDK2, serum glucose might be decreased via inhibiting the amount of pyruvate present in liver for gluconeogenesis. GCK activation also causes decrease of serum glucose amounts by helping glycogenesis and glycolysis via phosphorylation of glucose to glucose6-phosphate. Decrease in hyperlipidemia can be explained by control of protein targets NR5A2, the PPARs and RXRA which are responsible for lipid metabolism. PPARs have variety of actions in lipid metabolism via genes which control and participate in lipogenesis, TG generation, reverse cholesterol transport, lipolysis and FA oxidation. PPARG expression of cluster differentiation 36 (CD36) helps in clearing away the oxidized LDL through blood via macrophages, further PPARG stimulates expression of liver X receptor (LXR) which then stimulates the expression of reverse cholesterol transporter ABCA1 that liberates HDL into the blood stream, where cholesterol get concerted to bile salts in the liver and then excreted. Moreover PPARG promotes adipogenesis, making new adipocytes which can pick up extra lipids through plasma at the time promoting apoptosis of lipid –saturated adipocytes. In the liver PPARA helps in fatty acid (FA) oxidation, enhances FA uptake by escalating the expression of FA transport along with FA translocase, enhancing apolipoprotein A1 (Apo-A1, i.e HDL) reduces Apo-C2 (part of VLDL) and, enhancing LPL (helping in breaking of TG → FA) Like PPARA, PPARD stimulates FA oxidation via up regulating of the target gene carnitine palmitoyl transferase A1 and reduces TG amounts via down regulation of target protein angiopoietin –like 4 proteins which normally inhibits breaking and removal of TG [23]. Therapy with PPAR agonists hence will cause reduced cholesterol, TG, LDL, VLDL amounts at the same time escalating HDL amounts. NR5A2 is markedly expressed in liver which targets the bile synthesizing enzymes cholesterol 7 –alpha hydroxylase (CYP7A1) along with sterol 12 –alpha hydroxylase (CYP8B1). Rest of the target genes are mediators of cholesterol uptake and efflux, HDL synthesis, cholesterol exchange among lipoproteins, and FA generation. Therapy with NR5A2 agonists hence would help in decreasing hyperlipidemia. The targeting of proteins PTPN9, DPP4, HSD11B1, RBP4, FFAR1, and INSR would help in insulin liberation from the B-cells and enhance insulin sensitivity. This will then help in sustaining glucose homeostasis and thus decrease hyperglycemia.

Protein tyrosine phosphatase non receptor type 9 (PTPN9) interferes with the insulin signaling pathway and hence therapy utilizing inhibitors would cause insulin sensitization and enhance glucose homeostasis.

Half-life of the incretin hormones would be escalated by Inhibition of dipeptidyl peptidase (DPP4) and thus, result in escalated insulin secretion and give time to for blood glucose levels to touch normal levels. Compounds that have the ability of inhibiting hydroxysteroid Dehydrogenase 11 B1 (HSD11B1) can inhibit glucose synthesis by the liver and enhance glucose-dependent insulin sensitivity.

Enhanced levels of retinol binding protein 4 (RBP4) have a correlation with insulin resistance (IR) where RBP4 acts as an adipokine and thus interferes with insulin signaling and decreases glucose uptake in the muscles. RBP4 further assists glucose generation by the liver thus enhancing plasma glucose levels. Compounds thus having the capacity of binding RBP4 might interfere with its correlation with transthyretin, causing excessive clearance of the enhanced serum RBP4via the kidneys. Treatment with FFAR1 agonists will potentiate glucosedependent insulin secretion via the pancreatic B-cells and in the gastrointestinal tract (GIT) will help in the liberation of the incretin hormones. These are natural products from the terpenoid class and get synthesized with the use of mevalonic acid. They have small molecular weight and are nonpolar in nature, which makes them