Anti-Diabetic Activity of Natural Compounds

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Diabetes mellitus (DM) is a metabolic disease defined by a persistently high blood sugar level. There are numerous kinds of diabetes mellitus, but the two most common are type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune disease; it occurs due to the destruction of insulin-producing pancreatic β cells, and the patients are entirely reliant on exogenous insulin injection.

Keywords: diabetes mellitus ; natural compounds

1. Brief Overview of Diabetes Types

Diabetes mellitus (DM) is a metabolic disease defined by a persistently high blood sugar level. There are numerous kinds of diabetes mellitus, but the two most common are type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune disease; it occurs due to the destruction of insulin-producing pancreatic β cells, and the patients are entirely reliant on exogenous insulin injection. T2DM is caused by impaired insulin secretion, which generally occurs in the context of pre-existing insulin resistance [1][2].

Specific complications may occur faster and progress with early diagnosis and longer exposure to T1DM in children. T2DM is a complex disease dependent on a number of factors such as environmental, metabolic and genetic factors [3]. T2DM affects about 10% of the population, but diagnosing it and maintaining a controlled blood sugar level helps slow down the complications of diabetes [4]. The molecular mechanisms involved in T2DM are incompletely explained, but insulin resistance and defects in insulin secretion are the main causes of this disease [5]. Insulin resistance may be due to both obesity and neuroendocrine function [6].

Herbal medicines are still used in current times and are classified as complementary and alternative medicine. Many plants have anti-diabetic properties via modulating insulin production, cell insulin sensitivity, or glucose absorption. Additionally, to glycemic management, several plants showed promise in preventing other DM-related illnesses such as cardiovascular problems by lowering cholesterol levels and BMI [7]. Flavanone and polyphenols natural chemical groups were investigated as a possible therapy in T2DM or adjuvant in DM treatment. Curcumin, resveratrol, and carotenoid were the most commonly studied substances among these [8].

Natural compounds or plants may act on DM protein targets. These targets could be proteins involved in the metabolism and uptake of glucose, proteins that control insulin secretion, and proteins involved in pancreatic β cell development. Below we present some targets in DM, along with plants and natural compounds used in DM management.

2. Molecular Targets Involved in Diabetes Mellitus

Peroxisome proliferator activated receptor gamma (PPARγ) activity can prevent insulin resistance by increasing glucose uptake in adipocyte and muscle cells, which results in lowering of blood glucose levels. Moreover, PPARγ agonists reduce the inflammation mediators that promote insulin resistance and trigger an increase in circulating adiponectin levels with a positive outcome for insulin sensitivity and a decreasing effect on glucose production in the liver [9].

Glucose co-transporter (SGLT) is involved in insulin independent glucose reabsorption in nephrons. SGLT1 and SGLT2 are the main SGLT types, expressed in kidneys in a ratio of 1:10 [10]. The inhibition of SGLTs by gliflozin drugs reduces glucose reabsorption and the levels of glycated hemoglobin [11].

Glutamine:fructose-6-phosphate aminotransferase 1 (GFPT1) is the rate limiting enzyme in glucose metabolism by the hexosamine pathway (associated with impaired insulin secretion and insulin resistance) [12].

Glucokinase regulatory protein (GKRP) represents the endogenous inhibitor of glucokinase, an enzyme that regulates glucose uptake and glycogen synthesis and suppresses glucose production [13]. Glucokinase is involved in glucose homeostasis and is found in pancreatic β-cells and hepatocytes. This kinase stimulates insulin production in pancreatic cells in response to glucose and glucose absorption, glycogen synthesis, and storage in hepatocytes [14]. Hepatic glucokinase expression is reduced in insulin resistance but also T2DM, implying dysregulation of this biomarker [15]. In diet-induced obese mice, the effect of glucokinase activators reduced blood sugar levels [16].

3. Plants Involved in Diabetes Mellitus Management

Momordica charantia is a plant used in clinical trials that has a beneficial effect on T2DM [17]. Although it had no effect in acute episodes of hyperglycemia, long-term administration has managed to improve the parameters of patients in clinical trials [18]. The mode of action is not yet fully understood, but studies suggest altered insulin secretion in patients and improved insulin sensitivity by increasing adenosine monophosphate-activated protein kinase (AMPK) [19]. The main chemical compounds found in this medicinal plant are charantine, cucurbitan glycosides, momordicin and oleanolic acids [20][21]. In addition to the presence of natural compounds, *Momordica charantia* can synthesize peptides that can bind to the insulin receptor, lowering blood glucose levels. These peptides may help reduce the need for insulin and limit the side effects of antidiabetic drugs [22].

Trigonella foenum-graecum is a medicinal plant whose seeds contain compounds with therapeutic effects. The seeds of this plant can lower the rate of glucose absorption. They help control diabetes, but also reduce cholesterol, cardiovascular risk and other chronic diseases [23].

Gynura procumbens Merr. belongs to the Asteraceae family, and is a plant found in tropical countries that is used for the therapeutic treatment of inflammatory diseases (e.g., rheumatism), heart disease (e.g., hypertension) and diabetic diseases [24]. Studies on the solvent fractions of *G. procumbens* Merr evaluated the antioxidant and antidiabetic effects of the compounds in this plant. In studies on the HepG2 cell line and insulin resistance, *G. procumbens* fractions obtained with the highest phenol content favoured insulin absorption. The compounds with the highest activity in *G. procumbens* were kaempferol, quercitin, caffeoyl-O-hexoside caffeoylquinic acid, coumaroyl-O-hexoside and coumaroylquinic acid. Bioinformatics studies have shown strong molecular interactions between natural compounds and digestive enzymes, thus underlining the value of studying these compounds [25].

Helianthus tuberosus is a perennial plant with high resistance to stress, nutritional value and possible antidiabetic effects. This plant is an alternative to classic animal feed; it can produce a high amount of biomass, and its activity on animal digestion, antibacterial, anti-inflammatory and antioxidant effect is due to natural compounds [26].

4. Natural Compounds Involved in Diabetes Mellitus Management

Docosanol is a compound that belongs to the class of aliphatic alcohols, with proven antiviral activity [27]. However, molecular docking studies have shown that it is a candidate for inhibiting α-glucosidase and α-amylase [28]. In vitro and in vivo studies show that this compound can lower blood sugar levels [29].

Isorutarine is linked to the main target of antidiabetic drugs, α-glucosidase and α-amylase. The same targets are inhibited by actinodafine, a compound with antidiabetic activity [28]. The proposed molecular mechanism for this compound came from molecular docking studies, and its effectiveness has been proven by studies in laboratory animals. Additionally, this compound has high therapeutic potential in lowering blood sugar levels [30]. Nodakenin has an inhibitory effect on α-glucosidase, PTP1B, acetylcholinesterase and butyrylcholinesterase [31].

In in vitro studies, compounds such as neochlorogenic acid, chlorogenic acid, caffeic acid, 5-OA-(4-cumaroyl) -quinic acid, feruloylquinic acid, caffeoylquinic acid, isoxazolidine, and β-D-glucoside of salicylic acid showed antidiabetic activity, acting on α-amylase and α-glucosidase. Free radical scavenging and inhibition of diabetes-associated enzymes are dose-dependent, but according to a study by Mariadoss et al., phytocompounds could reduce blood sugar levels, triggering glucose uptake into insulin-resistant HepG2 cells [32].

Molecular docking studies on (4Z, 12Z)-cyclopentadeca-4, 12-dienone have shown that this compound can inhibit the action of enzymes aldose reductase, glucokinase, pyruvate dehydrogenase kinase, receptor-gamma, glycogen synthase kinase-3, and fructose-6-phosphate amidotransferase with a role in diabetes. This compound is a valid candidate for the development of new antidiabetic drugs due to the various molecular targets to which it may bind [33].

References

1. Katsarou, A.; Gudbjörnsdottir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Jacobsen, L.M.; Schatz, D.A.; Lernmark, A. Type 1 Diabetes Mellitus. Nat. Rev. Dis. Primer 2017, 3.
2. DeFronzo, R.A.; Ferrannini, E.; Groop, L.; Henry, R.R.; Herman, W.H.; Holst, J.J.; Hu, F.B.; Kahn, C.R.; Raz, I.; Shulman, G.I.; et al. Type 2 Diabetes Mellitus. Nat. Rev. Dis. Primer 2015, 1, 1–22.
3. Fletcher, B.; Gulanick, M.; Lamendola, C. Risk Factors for Type 2 Diabetes Mellitus. J. Cardiovasc. Nurs. 2002, 16, 17–23.
4. Taylor, S.I.; Yazdi, Z.S.; Beitelshees, A.L. Pharmacological Treatment of Hyperglycemia in Type 2 Diabetes. J. Clin. Investig. 2021, 131.
5. Quinn, L. Mechanisms in the Development of Type 2 Diabetes Mellitus. J. Cardiovasc. Nurs. 2002, 16, 1–16.
6. Chronic Inflammation in Fat Plays a Crucial Role in the Development of Obesity-Related Insulin Resistance. Available online: https://pubmed.ncbi.nlm.nih.gov/14679177/ (accessed on 12 October 2021).
7. Choudhury, H.; Pandey, M.; Hua, C.K.; Mun, C.S.; Jing, J.K.; Kong, L.; Ern, L.Y.; Ashraf, N.A.; Kit, S.W.; Yee, T.S.; et al. An Update on Natural Compounds in the Remedy of Diabetes Mellitus: A Systematic Review. J. Tradit. Complement. Med. 2017, 8, 361–376.
8. Yeung, A.W.K.; Tzvetkov, N.T.; Durazzo, A.; Lucarini, M.; Souto, E.B.; Santini, A.; Gan, R.-Y.; Jozwik, A.; Grzybek, W.; Horbańczuk, J.O.; et al. Natural Products in Diabetes Research: Quantitative Literature Analysis. Nat. Prod. Res. 2020, 0, 1–15.
9. Monsalve, F.A.; Pyarasani, R.D.; Delgado-Lopez, F.; Moore-Carrasco, R. Peroxisome Proliferator-Activated Receptor Targets for the Treatment of Metabolic Diseases. Mediators Inflamm. 2013, 2013, 1–18.
10. Harada, N.; Inagaki, N. Role of Sodium-Glucose Transporters in Glucose Uptake of the Intestine and Kidney. J. Diabetes Investig. 2012, 3, 352–353.
11. Kitamura, K.; Hayashi, K.; Ito, S.; Hoshina, Y.; Sakai, M.; Yoshino, K.; Endo, K.; Fujitani, S.; Suzuki, T. Effects of SGLT2 Inhibitors on EGFR in Type 2 Diabetic Patients—the Role of Antidiabetic and Antihypertensive Medications. Hypertens. Res. 2021, 44, 508–517.
12. Elbein, S.C.; Zheng, H.; Jia, Y.; Chu, W.; Cooper, J.J.; Hale, T.; Zhang, Z. Molecular Screening of the Human Glutamine–Fructose-6-Phosphate Amidotransferase 1 (GFPT1) Gene and Association Studies with Diabetes and Diabetic Nephropathy. Mol. Genet. Metab. 2004, 82, 321–328.
13. Lloyd, D.J.; St Jean, D.J.; Kurzeja, R.J.M.; Wahl, R.C.; Michelsen, K.; Cupples, R.; Chen, M.; Wu, J.; Sivits, G.; Helmering, J.; et al. Antidiabetic Effects of Glucokinase Regulatory Protein Small-Molecule Disruptors. Nature 2013, 504, 437–440.
14. Toulis, K.A.; Nirantharakumar, K.; Pourzitaki, C.; Barnett, A.H.; Tahrani, A.A. Glucokinase Activators for Type 2 Diabetes: Challenges and Future Developments. Drugs 2020, 80, 467–475.
15. Luna-Vital, D.A.; Gonzalez de Mejia, E. Anthocyanins from Purple Corn Activate Free Fatty Acid-Receptor 1 and Glucokinase Enhancing in Vitro Insulin Secretion and Hepatic Glucose Uptake. PLOS ONE 2018, 13, e0200449.
16. Xu, J.; Lin, S.; Myers, R.W.; Trujillo, M.E.; Pachanski, M.J.; Malkani, S.; Chen, H.-S.; Chen, Z.; Campbell, B.; Eiermann, G.J.; et al. Discovery of Orally Active Hepatoselective Glucokinase Activators for Treatment of Type II Diabetes Mellitus. Bioorg. Med. Chem. Lett. 2017, 27, 2063–2068.
17. Kim, S.K.; Jung, J.; Jung, J.H.; Yoon, N.; Kang, S.S.; Roh, G.S.; Hahm, J.R. Hypoglycemic Efficacy and Safety of Momordica Charantia (Bitter Melon) in Patients with Type 2 Diabetes Mellitus. Complement. Ther. Med. 2020, 52, 102524.
18. Kasbia, G.S.; Arnason, J.T.; Imbeault, P. No Effect of Acute, Single Dose Oral Administration of Momordica Charantia Linn., on Glycemia, Energy Expenditure and Appetite: A Pilot Study in Non-Diabetic Overweight Men. J. Ethnopharmacol. 2009, 126, 127–133.
19. Chaturvedi, P. Antidiabetic Potentials of Momordica Charantia: Multiple Mechanisms Behind the Effects. J. Med. Food 2012, 15, 101–107.
20. Cortez-Navarrete, M.; Martínez-Abundis, E.; Pérez-Rubio, K.G.; González-Ortiz, M.; Méndez-Del Villar, M. Momordica Charantia Administration Improves Insulin Secretion in Type 2 Diabetes Mellitus. J. Med. Food 2018, 21, 672–677.
21. George, S.; Chaturvedi, P. Momordica Charantia Maintains Normal Glucose Levels and Lipid Profiles and Prevents Oxidative Stress in Diabetic Rats Subjected to Chronic Sucrose Load. J. Med. Food. 2010, 13, pp. 520–527.

22. Arif, R.; Ahmad, S.; Mustafa, G.; Mahrosh, H.S.; Ali, M.; Tahir ul Qamar, M.; Dar, H.R. Molecular Docking and Simulation Studies of Antidiabetic Agents Devised from Hypoglycemic Polypeptide-P of Momordica Charantia. BioMed Res. Int. 2021, 2021, e5561129.
23. Sun, W.; Shahrajabian, M.H.; Cheng, Q. Fenugreek Cultivation with Emphasis on Historical Aspects and Its Uses in Traditional Medicine and Modern Pharmaceutical Science. Mini Rev. Med. Chem. 2021, 21, 724–730.
24. Tan, H.-L.; Chan, K.-G.; Pusparajah, P.; Lee, L.-H.; Goh, B.-H. Gynura Procumbens: An Overview of the Biological Activities. Front. Pharmacol. 2016, 7, 52.
25. Sathiyaseelan, A.; Park, S.; Saravanakumar, K.; Mariadoss, A.V.A.; Wang, M.-H. Evaluation of Phytochemicals, Antioxidants, and Antidiabetic Efficacy of Various Solvent Fractions of Gynura Procumbens (Lour.) Merr. Process Biochem. 2021, 111, 51–62.
26. Wang, Y.; Zhao, Y.; Xue, F.; Nan, X.; Wang, H.; Hua, D.; Liu, J.; Yang, L.; Jiang, L.; Xiong, B. Nutritional Value, Bioactivity, and Application Potential of Jerusalem Artichoke (Helianthus Tuberosus L.) as a Neotype Feed Resource. Anim. Nutr. 2020, 6, 429–437.
27. Docosanol. Available online: https://go.drugbank.com/drugs/DB00632 (accessed on 6 October 2021).
28. Riyaphan, J.; Jhong, C.-H.; Lin, S.-R.; Chang, C.-H.; Tsai, M.-J.; Lee, D.-N.; Sung, P.-J.; Leong, M.K.; Weng, C.-F. Hypoglycemic Efficacy of Docking Selected Natural Compounds against α-Glucosidase and α-Amylase. Molecules 2018, 23, 2260.
29. Kaleshkumar, K.; Rajaram, R.; Gayathri, N.; Sivasudha, T.; Arun, G.; Archunan, G.; Gulyás, B.; Padmanabhan, P. Muscle Extract of Arothron Immaculatus Regulates the Blood Glucose Level and the Antioxidant System in High-Fat Diet and Streptozotocin Induced Diabetic Rats. Bioorganic Chem. 2019, 90, 103072.
30. Jhong, C.-H.; Riyaphan, J.; Lin, S.-H.; Chia, Y.-C.; Weng, C.-F. Screening Alpha-Glucosidase and Alpha-Amylase Inhibitors from Natural Compounds by Molecular Docking in Silico. BioFactors Oxf. Engl. 2015, 41, 242–251.
31. Gao, Q.; Jeon, S.J.; Jung, H.A.; Lee, H.E.; Park, S.J.; Lee, Y.; Lee, Y.; Ko, S.Y.; Kim, B.; Choi, J.S.; et al. Nodakenin Enhances Cognitive Function and Adult Hippocampal Neurogenesis in Mice. Neurochem. Res. 2015, 40, 1438–1447.
32. Mariadoss, A.V.A.; Park, S.; Saravanakumar, K.; Sathiyaseelan, A.; Wang, M.-H. Ethyl Acetate Fraction of Helianthus Tuberosus L. Induces Anti-Diabetic, and Wound-Healing Activities in Insulin-Resistant Human Liver Cancer and Mouse Fibroblast Cells. Antioxidants 2021, 10, 99.
33. Natarajan, A.; Sugumar, S.; Bitragunta, S.; Balasubramanyan, N. Molecular Docking Studies of (4Z, 12Z)-Cyclopentadeca-4, 12-Dienone from Grewia Hirsuta with Some Targets Related to Type 2 Diabetes. BMC Complement. Altern. Med. 2015, 15, 73.