International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Therapeutic Mechanism of Phytochemicals in T2DM Control: Scope for an Integrative Care

S S Sreenivas
Chief Technical Officer (Rt), ICAR-CTRI Research Station, Hunsur, Karnataka, 571105
Corresponding author: vas_sss@yahoo.co.in

Abstract*—Diabetes mellitus (DM) is currently a global public health risk with around 830 million diabetic population. The condition is more alarming in low and middle income countries. T2DM condition is often leads to serious complications like nephropathy, retinopathy, neuropathy, dyslipidemia and cardiovascular diseases if not treated. Accessibility to medical aid, treatment costs with conventional drugs and awareness about the DM are critical in addressing this health issue. In order to avoid late-stage complications use of alternate methods like plant-based dietary habits to manage pre-diabetic and T2DM conditions is gaining popularity. Plants are known to exhibit antihyperglycemic activity are being integrated in the diet without any side effects. Several botanicals are popular and being used as traditional medicine for many ailments. Plant parts, vi., root, stem. leaves, flowers, fruits and seeds are of immense medicinal value. Studies with many plant species have conclusively proved their medicinal properties. Several investigations have been on animal models with few scattered clinical studies to prove their effectiveness. However, there is a big lacuna in translating the knowledge from animal experiments to their effectiveness in clinical studies. The paper attempts to review the available information reported on the therapeutic mechanism of promising phytochemicals against hyperglycemic condition.*

Keywords— *Diabetes mellitus; T2DM; phytochemicals; therapeutic mechanism*

I. INTRODUCTION

Diabetes mellitus is of two major classes- type 1 or insulin dependent, and type 2 or non-insulin dependent. In type 1 diabetes there is almost complete loss of insulin producing cells, while in type 2 diabetes the major manifestations are insensitivity of the pancreatic β-cells to glucose stimulated insulin release and the impairment of skeletal muscle cells to insulin stimulated glucose entry (insulin resistance). Both types of diabetes un-checked lead to serious complications like nephropathy, retinopathy, neuropathy, dyslipidemia and cardiovascular diseases (Deshpande *et al.*, 2008; Ghorbani *et al.*, 2010). T2DM patients are also, at an increased risk of developing Alzheimer's disease due to oxidative stress, inflammation, and mitochondrial dysfunction. According to IDF (2024)10.5% of the adult population in the age group 20-79 years has diabetes, with almost 50% of population unaware of the condition. Diabetes is more common in low- and middle-income nations. Data shows that 14% of adults were living with diabetes, an increase from 7% in 1990. (UN, 2024). According to ID 3 in 4 adults with diabetes live in low and middle-income countries. Comprising approximately 90% of all diabetes cases, type 2 diabetes is the most frequently encountered type of diabetes. Apart from drugs it is seen that patients do take precaution through nutritive plant-based dietary habits to manage T2DM effectively. Botanical species are well documented for their medicinal value and advocated as therapy in traditional medicine. Several plant-based derivatives have been extensively reported to have antihyperglycemic activity. The present article on how these plant-constituents affect the pathophysiology of T2DM and to summarize the mechanism involved in the antiglycemic activity for a better understanding.

II. T2DM OR NON-INSULIN DEPENDENT DIABETES

In recent years there has been alarming increase of T2DM in poor and under developed countries (Whiting *et al*., 2011; Wild *et al*., 2004; Chakraborty and Das, 2016; Sarker *et al.*, 2022). While insulin is the only therapy for T1DM, patients with T2DM rely primarily on one or more of a range of oral antihyperglycemic drugs. Common class of drugs prescribed for T2DM are insulin secretagogues (sulphonylureas and meglitinide analogues), insulin sensitizers (metformin, rosiglitazone, pioglitazone, D-chiro-inositol), α-glucosidase inhibitors (acarbose, miglitol, voglibose and emiglitate) are widely used to treat people with type 2 diabetes mellitus. While new class of drugs such as exenatide, liraglutide and DPP-4 inhibitors increase GLP-1 lower serum glucose levels and thereby manage metabolism in affected patients. The first available DPP-4 inhibitors are sitagliptin, dapagliflozin and vildagliptin. (Hui *et al*., 2005; Boli, 2006; Modi, 2007; Garber and Spann, 2008; Main Penalver *et a*l., 2016).

III. PLANT METABOLITES IN THE CONTROL OF T2DM

Botanicals are known for their medicinal properties in traditional medicine as herbal preparations. Several plant-derived drugs have been validated as potent antidiabetics which include flavonoids (queretin, neringerin and chrysin), alkaloids (berberin, catharenthine and vindolin), glycosides and saponins (triterpenoid and steroidal glycosides such as charantin, lactucain C, β-sitosterol and gymnemic acid), glycolipids, dietary fibres, imidazole compounds, polysaccharides, peptidoglycans, carbohydrates and amino acids (Covington, 2001; Gaikad *et al*., 2014; Chen *et al*., 2015). Dietary fiber-rich vegetables and fruits, in particular, reported to regulate hyperglycemia and mitigate diabetic complications are gaining importance (Jung *et al*., 2014). The

S S Sreenivas, "Therapeutic mechanism of phytochemicals in T2DM control: Scope for an integrative care," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 8, Issue 1, pp. 23-25, 2024.

first understanding on phytochemical mediated antiglycemic mechanism lead to development of drug Metformin based on the use of *Galega officinalis* rich in guanidine which is toxic. In 1920 the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe (Evans and Bahng, 2014). Thus, botanicals with active principles have became source for the discovery of new drug templates (Salimifar *et al*., 2013; Yaribeygi *et al*., 2021). A better understanding on how these plant-derived constituents affect the pathophysiology of T2DM helps to prevent this disease in a better manner (Ansari *et al*., 2022;2023; Clemente-Suárez *et al*., 2023)

IV. Plant Metabolites and Regulatory Mechanism

Diabetes is due to disturbed carbohydrate, fat and protein metabolism leading to the less production of insulin or resistance to its action. Phytoconstituents regulate intermediates of different metabolic pathways as antihyperglycemic. Broadly the regulating mechanism can be as below;

1. Insulin-mimetic mechanism effect improves glucose uptake in peripheral tissues, insulin secretion and β cell number in the pancreas (Dey, Attele and Yuan 2002).Insulin-like bioactive polypeptide-p, in Bitter Melon (*Momordica charantia*) (Basch *et al*., 2003; Evans 2003; Grover and Yadav 2004; Krawinkel and Keding 2006; Leung *et al*., 2009), 4-hydroxyisoleucine in Fenugreek (*Trigonella foenum*) (Broca *et al.*, 1999, 2000) and polyphenol type-A polymers in *Cinnamomum cassia* (Jarvill-Taylor *et al*., 2001; Anderson *et al*., 2004) are reported to have glucose-lowering effect. The mechanism of action is insulin-mimetic effect improving glucose uptake in peripheral tissues, insulin secretion and β cell number in the pancreas (Dey, Attele, and Yuan 2002). Similarly, *Coccinia indica* is also, reported to have insulin-mimetic properties (Kamble *et al*., 1996;1998; Kuppurajan *et al*., 1986). Insulin sensitivity and enhancement of insulin secretion is reported in okra (*Abelmoschus esculentus)* (Pannerselvam *et al*., 2011)
2. Secretagouge (Karunanayake *et al*., 1984), help in enhancing insulin production and insulin secretion and insulin sensitivity, and increased GLUT4 expression (Bever and Hand, 1979; Alam *et al*., 2019; Chowdhari *et al*., 2019; Pingali *et al*., 2020; Eidi *et al*.,2006; Liu *et al*., 2012) and inhibit α-glucosidase.
3. A water-soluble fiber in *Aloe vera* gel of the leaves reported to have hypoglycemic and insulin-sensitizing actions (Vuksan *et al.*,1999; 2000).
4. Inhibiting the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), two enzymes associated with insulin resistance and metabolic syndrome are also reported. Inhibiting activity of α-amylase and α-glucosidase enzymes (Rao *et al*.,2021) delay the time of absorption of glucose.
5. Normalizing the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase (Raman-Ramos *et al*., 1995; Kumari *et al*., 1995),
6. Blocking of glucose absorption, inhibition of glucose-6-phosphatase besides fructose-1, 6- biphosphatase in the liver and stimulation of hepatic glucose- 6-phosphate dehydrogenase activities (Shibib *et al*., 1993),
7. Improving glucose metabolism and increase glucose tolerance (Gupta *et al*.,1967).
8. Free radicals damage cellular molecules, DNA, proteins and lipids leading to altered cellular functions. Antioxidants are capable of neutralizing free radicals are effective in preventing diabetes and reducing the severity of diabetic complications (Kubish *et al*., 1997; Naziroglu and Cay, 2001; Lipinski, 2001).

V. Conclusion

Although findings including clinical studies, have reported beneficial effects of various plants, the data is still limited and further studies are needed to pin point the advantage in treating T2DM. A caution is needed as phytoconstituents may exert synergistic effect in addition to antidiabetic property. A thorough knowledge on the synergistic role of these with chemical drugs is also, to be studied. Nevertheless, phytochemicals provide opportunity for developing an integrated approach to manage T2DM more effectively at a affordable cost.

References

[1] F.Alam, Z. Shafique, S.T. Amjad, M. Bin Asad. Enzymes Inhibitors from Natural Sources with Antidiabetic Activity: A Review. *Phytother. Res.* PTR, 33, 41–54, 2019,

[2] R.A. Anderson, C.L. Broadhurst, M.M. Polansky, W.F. Schmidt, A.Khan, V.P.Flanagan, D.J.Graves. Isolation and characteri-sation of polyphenol Type-A polymers from cinnamon with insulin-like biological activity. J *Agr Food Chem.*,52(1): 65-70,2004.

[3] P. Ansari, S,Akther, J.T. Khan, S.S.Islam, M.S.R.Masud, A.Rahman, V.Seidel, Y.H.A.Abdel-Wahab, Hyperglycaemia-Linked Diabetic Foot Complications and Their Management Using Conventional and Alternative Therapies. *Appl. Sci. , 12*, 11777, 2022.

[4] P.Ansari, J.F. Samia,J.T.Khan,M.R.Rafi, M.S. Rahman, A.B. Rahman, Y.H.R.Abdel-Wahab, V. Seidel, Protective Effects of Medicinal Plant-Based Foods against Diabetes: A Review on Pharmacology, Phytochemistry, and Molecular Mechanisms. associated complications. *Curr. Topics Med. Chem.,16*, 2532–2542, 2016.

[5] E. Basch, S. Gabardi and C Ulbricht. Bitter Melon (*Momordica charantia*): A Review of Efficacy and Safety, *American Journal of Health-System Pharmacy*, 60, No. 4, , pp. 356-359, 2003.

[6] B.O.Bever and G.R.Zahnd. Plants with oral hypog-lycemic action. *Quart. J. Crude Drug Res.*, 17, 139–146, 1979.

[7] G.B.Bolli. Insulin treatment in type 1 diabetes. *Endocr. Pract*., 12 (Suppl. S1), 105–109,2006

[8] Broca Christophe, René Gross, Pierre Petit,Yves Sauvaire,Michèle Manteghetti, Michel Tournier,Pellegrino Masiello,Ramon Gomis, and Gérard Ribes. 4-Hydroxyisoleucine: experimental evidence of its insulinotropic and antidiabetic properties. American *Journal of Physiology-Endocrinology and Metabolism.*, 277:4, E617-E623.1999.

[9] C.Chakraborty, S.Das, Dynamics of Diabetes & Obesity: An Alarming Situation in the Developing Countries in *Asia. Mini Rev. Med. Chem*., 16, 1258–1268,2016.

[10] S.Chaudhari,S.Zambad, M.Ali. Effect of Aqueous Extract of *Azadirachta indica* Leaves on Pharmacokinetics and Pharmacodynamics of Glipizide. *Drug Metab. Lett. , 13*, 19–24,2019.

[11] J.Chen, S.Mangelinckx, A.Adams, Z.Wang, W.Li, N.De Kimpe. Natural flavonoids as potential herbal medication for the treatment of diabetes mellitus and its complications. *Nat. Prod. Commun*, *10*, 187–200,2015.

[12] V.J.Clemente-Suárez, A.I. Beltrán-Velasco, L.Redondo-Florez.Martín-Rodríguez, A. Tornero-Aguilera, J.F. Global Impacts of Western Diet and Its Effects on Metabolism and Health: A Narrative Review. *Nutrients. , 15*, 2749,2023.

[13] A.D.Deshpande, M. Harris-Hayes, M. Schootman. Epidemiology of diabetes and diabetes-related complications. *Phys. Ther.*, v.88, p.1254-1264, 2008.
[14] L.Dey, A.S.Attele,C.S.Yuan, Alternative therapies for type2 diabetes. *Altern. Med. Rev*., 7, 45–8,2002.
[15] A.Eidi, M. Eidi,E.Esmaeili. Antidiabetic Effect of Garlic (*Allium sativum* L.) in Normal and Streptozotocin-Induced Diabetic Rats. *Phytomedicine., 13*, 624–629,2006.
[16] J. L. Evans and M. Bahng. *Non-pharmaceutica*l *Intervention Options for type 2 Diabetes: Diets and Dietary Supplements (Botanicals, Antioxidants, and Minerals), Eds;* De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM *et al.* South Dartmouth MA: MDText.com, Inc.2014.
[17] S.Gaikwad, G.Krishna Mohan,M. Sandhya Rani. Phytochemicals for diabetes management. *Pharm. Crops. 5*, 11–28, 2014.
[18] A.J.Garber,S.J.Spann. An overview of incretin clinical trials. *J Fam Pract.*, 57(9 Suppl):S10-8,2008
[19] A. Ghorbani,H. Rakshsadeh. *The most effective herbs for diabetes*. *Mashhad:* Mashhad University of Medical Sciences Pub, p.21-127, 2012.
[20] J.K.Grover,S.P.Yadav,V.Vats. Medicinal plants of India with anti-diabetic potential. *J.* Ethnopharmacol. , *81*, 81–100,2002.
[21] J.K, Grover, S.P.Yadav.Pharmacological actions and potential uses of *Momordica charantia*: A review.*J.Ethnopharmacol*.,93(1):123-32.2004.
[22] D.Gupta,J.Raju and N.Z.Baquer. Modulation of some gluconeogenic enzyme activities in diabetic rat liver and kidney: effect of antidiabetic compounds. I*ndian J. Expt. Biol*., 37, 196–199, 1999.
[23] H.Hui,X.Zhao, R.Perfetti. Structure and function studies of glucagon-like peptide-1 (GLP-1): the designing of a novel pharmacological agent for the treatment of diabetes. *Diabetes Metab Res Rev.*,21(4):313-331. 2005.
[24] International Diabetes Federation 2024.https://idf.org
[25] K.J.Jarvill-Taylor, R.AAnderson and D.J.Graves. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. *J Am Coll Nutr*., 20(4): 327-336,2001.
[26] H.Jung, Y.Lim, E.Kim. Therapeutic Phytogenic Compounds for Obesity and Diabetes. *Int. J. Mol. Sci*., 15, 21505–21537,2014.
[27] S.M.Kamble, G. S, Jyotishi, P.L.Kamlakar, S.M.Vaidya. Efficacy of *Coccinia indica* W.& A in diabetes mellitus. *J Res Ayurveda Siddha*, XVII:77–84, 1996.
[28] S.M.Kamble. P.L.Kamlakar, S. Vaidya, V.D.Bambole. Influence of *Coccinia indica* on certain enzymes in glycolytic and lipolytic pathway in human diabetes. *In dian J Med Sci*., 52:143–146, 1998.
[29] H.M.Kubish,J.Vang,T.M.Bray and J.P.Phillips.Targeted over expression of Cu/Zn superoxide dismutase protects pancreatic beta cells against oxidative stress. *Diabetes*, 46, 1563–1566, 1997.
[30] K. Kumari, B.C.Mathew and K.T. Augusti. Antidiabetic and hypolipidaemic effects of S-methyl cysteine sulfoxide, isolated from *Allium cepa* Linn. *Ind. J. Biochem. Biophys*., 32, 49–54, 1995.
[31] K. Kuppurajan, C. Seshadri, R. Revathi S. Venkataraghavah. Hypoglycaemic effect of *Coccinia indica* in diabetes mellitus. *Nagarjun*, 29:1–4, 1986
[32] Lawrence Leung, Richard Birtwhistle, Jyoti Kotecha, Susan Hannah, Sharon Cuthbertson.Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. *Br J Nutr.*,102(12):1703-8,2009
[33] B.Lipinski. Pathophysiology of oxidative stress in diabetes mellitus. *J. Diabet. Complications*, 15, 203–210, 2001.
[34] C.T.Liu, T.W.Hsu, K.M.Chen,Y.P.Tan, C.K.Lii, L.Y Sheen. The Antidiabetic Effect of Garlic Oil is Associated with Ameliorated Oxidative Stress but Not Ameliorated Level of Pro-inflammatory Cytokines in Skeletal Muscle of Streptozotocin-Induced Diabetic Rats. *J. Traditional and Complementary Medicine*., Volume 2, Issue 2, April–June , Pages 135-144,2012.
[35] J.J.Marín-Peñalver, I. Martín-Timón, C, Sevillano-Collantes, .F.J. Del Cañizo-Gómez. Update on the treatment of type 2 diabetes mellitus. *World J. Diabetes*, 7, 354–395,2016.
[36] Marín-Peñalver. Juan Jose, Iciar Martín-Timon , Cristina Sevillano-Collantes, Francisco Javier Del Cañizo-Gomez. Update on the treatment of type 2 diabetes mellitus. *World J Diabetes*., 7(17):354-95,2016.
[37] Michael B Krawinkel, Gudrun B Keding. Bitter gourd (*Momordica c*harantia): A dietary approach to hyperglycemia. *Nutr Rev*.. 64(7 Pt 1):331-7,2006.
[38] P.Modi.Diabetes beyond insulin: review of new drugs for treatment of diabetes mellitus. *Curr Drug Discov Technol.*, 4(1):39-47.2007
[39] M. Naziroglu and M. Cay.Protective role of intra-peritoneally administered vitamin E and selenium on the oxidative defense mechanisms in rats with diabetes induced by streptozotocin. *Biol. Stress Elem. Res.*, 47, 475–488, 2001.
[40] K. Panneerselvam, S. Ramachandran, V. Sabitha, K.R. Naveen. Antidiabetic and antihyperlipidemic potential of *Abelmoschus esculentus* (L.) Moench. in streptozotocin-induced diabetic rats. *J. Pharm. Bioallied Sci*., 3: 397–402,.2011
[41] U .Pingali, M.A. Ali, S. Gundagani, C. Nutalapati. Evaluation of the Effect of an Aqueous Extract of *Azadirachta indica* (Neem) Leaves and Twigs on Glycemic Control, Endothelial Dysfunction and Systemic Inflammation in Subjects with Type 2 Diabetes Mellitus-A Randomized, Double-Blind, Placebo-Controlled Clinical Study. *Diabetes Metab. Syndr. Obes. Targets Ther.*, 13, 4401–4412,2020.
[42] A.G.Rao, K.SNaik, A.G.Unnikrishnan, J.Joseph. Efficacy of Green Jackfruit Flour as a Medical Nutrition Therapy Replacing Rice or Wheat in Patients with Type 2 Diabetes Mellitus: A Randomized, Double-Blind, Placebo-Controlled Study. Nutr. Diabetes. Rats. *J. Tradit. Complement. Med., 2*, 135–144,2012.
[43] R. Roman-Ramos, J.L. Flores - Saenz and F .J. Alaricon - Aguilar. Antihyperglycemic effect of some edible plants. *J. Ethnopharmacol*., 48, 25–32, 1995.
[44] M.Salimifar, Z.Fatehi-Hassanabad, M. Fatehi. A Review on Natural Products for Controlling Type 2 Diabetes with an Emphasis on Their Mechanisms of Actions. *Curr. Diabetes Rev*., 9, 402–411.2013.
[45] A.R.Sarker,M. Khanam,. Socio-economic Inequalities in Diabetes and Prediabetes Among Bangladeshi Adults. *Diabetol. Int., 13*, 421–435,2022.
[46] B. A.Shibib, L. A.Khan and R. Rahman. Hypoglycaemic activity of *Coccinia indica* and *Momordica charantia* in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6- bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose- 6-phosphate dehydrogenase. *Biochem. J.*, 292, 267–270,1993.
[47] V.Vuksan, J.L.Sievenpiper, V.Y.Koo. American ginseng (*Panax quinquefolius* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch Intern Med*.,160: 1009–1013,2000.
[48] D.R.Whiting, L.Guariguata, C. Weil, J. Shaw, IDF Diabetes Atlas: Global Estimates of the Prevalence of Diabetes for 2011 and 2030. *Diabetes Res. Clin. Pract.*, 94, 311–321,2011.
[49] S.Wild, G.Roglic, A.Green, R.Sicree, H. King. Global Prevalence of Diabetes. *Diabetes Care.*, 27, 1047–1053.2004.
[50] United Nations. 2024. https://www.un.org › observances › diabetes-day
[51] Yaribeygi, H.; Sathyapalan, T.; Jamialahmadi, T.; Sahebkar, A. Natural Insulin Sensitizers for the Management of Diabetes Mellitus: A Review of Possible Molecular Mechanisms. *Adv. Exp. Med. Biol*., *1328*, 401–410, 2021.