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ANTI-DIABETICS: A CRITICAL OVERVIEW

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Abstract

The diabetes is recently developed as a most challenging disease to cure while we are following the modern life style along with the issues related to the chemotherapeutics known till date. The currently used anti-diabetic drugs have number of setback related to it, several known side effects includes lipid lowering, increase obsesses and immediate sugar lowering. These challenges have caused an alarm in the scientific community. Subsequently, there is an urgent need for the development of new drug molecules with newer targets and with an alternative mechanism of action. Since the last 50 years, the same long-duration, multidrug treatment plan is being followed for the treatment of diabeties. The objective of this review article is to critically analyze the antidiabetic potential of various classes of compounds (quinoline, diamine, quinolone, fluoroquinolone, quinone, nitroimidazole, terpenoid, isonicotinyl, oxazolidinone, pyrimidine, and purine), their possibility to be a future drug candidate, and latest information on the clinical status of some novel anti-diabetic compounds.

Keywords: Anti-diabetics,quinolone, Imidazole, Pyrimidine.

Introduction

Diabetes is the disease when the body does not produce or properly utilize insulin. Insulin is basically a hormone that converts sugar, starch and other food ingredients into energy which is utilized for the daily need of life by the body. The cause of diabetes is still a mystery, although both genetics and environmental factors might be the major role player for the disease, such as obesity and lack of physical exercise. Diabetes mellitus and glucose intolerance are common in adolescent and adult patients with cystic fibrosis and it is consistently associated with pancreatic exocrine dysfunction (mal-absorption). The prevalence of the disease in patients over 20 years of age may be as high as 53%. The major types of diabetes include type-I and type-II diabetes.

An estimated 347 million people worldwide have diabetes mellitus (DM), and the numbers are increasing globally with more than 80% of diabetes deaths occurring in low- and middle-income countries.135 Vanadium salts and coordination compounds have demonstrated various insulin-enhancing and antidiabetic effects; although they are not able to fundamentally substitute for the insulin paucity in type I diabetes, they can manage blood sugar levels in type II diabetes patients in a convenient oral formulation.136 In 1899, Lyonnet recorded that the administration of sodium vanadate to his diabetes patients had a positive effect on their health.137 In 1977, Josephson et al. realized that vanadate has an inhibitory effect toward phosphatases.138 In 1985, McNeill and Diabetes mellitus encompasses several diseases characterized by chronic hyperglycemia with disturbances in fat, carbohydrate and protein metabolism and caused due to defect in insulin secretion and/or action. According to WHO, in 2005, about 194 millions population were affected with diabetes and by 2050, expected to have almost 330 million diabetics throughout the world and half of them will be Asians and Pacific Islanders. India has currently 30 million diabetics and expected to have 80 million diabetics in next twenty years. In 2005, about 1.1 million people died of diabetes. So there is an urgent need to rectify the epidemic of diabetes.

Type-I diabetes, also known as juvenile-onset diabetes (previously referred to as insulin dependent diabetes mellitus or IDDM), is due to autoimmune destruction of pancreatic □-cells resulting in the inability of the pancreas to produce insulin. It is caused by auto-immune, genetic and/or environmental factors and accounts for the 5-10% of all reported cases in the western world. It usually develops before the age of 40 with the most cases presenting before the age of 20.

Type-II diabetes or adult-onset diabetes (previously referred to as non-insulin dependent diabetes mellitus or NIDDM), accounts for over 90% of the diabetic cases reported in the western world. In general, individuals suffering from type-II diabetes produce sufficient amount of insulin or ineffective insulin. Genetic predisposition and environmental factors contribute to its development and risk factors include obesity, dyslipidemia and cardiovascular risks. Other types of diabetes are much less frequent and include gestational diabetes, drug induced diabetes and diabetes secondary to illness or infection. Type-II is much more prevalent than other types, develops in middle or later life. Typically insulin resistance is an early feature of the condition, which is initially compensated in part by increased production of insulin by pancreatic □-cells (hyperinsulinaemia). Subsequently as their □-cells become exhausted, the combined effects of insulin resistance and impaired insulin secretion reduces insulin mediated glucose uptake and utilization by skeletal muscle, and prevent insulin-mediated suppression of hepatic glucose output. Continuing deterioration of endocrine control exacerbates these metabolic disturbances and increases the hyperglycemia. This presents a moving therapeutic target that requires a range of different agents to address different features of the disease at different stages of its natural history.

Treatment: Some patients can be controlled for some time on oral hypoglycemic agents, although most patients are best treated with insulin. At present, therapy for type-II diabetes relies mainly on several approaches intended to reduce the hyperglycemia itself.

Table-1: Current therapeutic agents for type-II diabetes:

Drug class	Molecular target	Site(s) of action	Adverse events
Insulin	Insulin receptor	Liver, muscle, fat	Hypoglycemia, weight gain
Sulphonylureas (e.g. libenclamide) plus nateglinide and repaglinide	SU receptor/ K+ ATP channel	Pancreatic β-cell	Hypoglycemia, weight gain
Metformin-biguanides	Unknown	Liver (muscle)	Gastrointestinal disturbances, lactic acidosis

Acarbose	α-glucosidase	Intestine	Gastrointestinal disturbances
Rosiglitazone, Pioglitazone-thiazolidinediones	PPARγ	Fat, muscle, liver	Weight gain, Anaemia, oedema,

Sulphonylureas increase insulin release from pancreatic islets; metformin acts to reduce hepatic glucose production; peroxisome proliferator-activated receptor-γ (PPARγ) agonists (thiazolidinediones) which enhance insulin action; α-glucosidase inhibitors interfere with gut glucose absorption and insulin itself suppresses glucose production and augments glucose utilization (Table: 1.1). These therapies have limited efficacy, limited tolerability and significant mechanism-based side effects. Thus, newer approaches are desperately needed. Several mechanistic categories for new therapeutic approaches can be considered. First are approaches aimed at reducing excessive glucose production by the liver; second, mechanisms to augment glucose-stimulated insulin secretion; third, specific molecular targets in the insulin signaling pathway and fourth, new approaches to obesity and altered lipid metabolism, which offer the prospect of net improvements in insulin action or secretion.

The liver is largely responsible for unrestrained glucose production through gluconeogenesis and glycogenolysis. Potential drug targets that modulate these processes include the glucagon receptor (antagonists), glycogen phosphorylase (inhibitors) and other rate-controlling enzymes such as glucose-6-phosphatase and fructose-1, 6-bisphosphatase (inhibitors). Defective glucose-stimulated insulin secretion by pancreatic islet β-cells could be alleviated with recombinant glucagon-like peptide 1 (GLP-1) or agonists of the GLP-1 receptor. To reduce insulin resistance, enhanced insulin action in liver and muscle (and fat) might be achieved with small-molecule activators of the insulin receptor or inhibitors of protein tyrosine phosphatase (PTP)-1B.

Nature: Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The ethnobotanical information reports that about 800 plants may possess anti-diabetic potential.[i]

Amongst these are flavonoids, alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids and amino acids. Even the discovery of widely used hypo glycemic drug, metformin came from traditional approach using *Galega officinalis*.[ii] Thus, plants are a potential source of anti-diabetic drugs. Herein, is presented a precise description of naturally occurring compounds possessing potential antihyperglycemic action against specific drug targets.

Targeting the insulin signaling pathway: The recent discovery of a small-molecule natural-product derivative that mediates selective activation of the insulin receptor is encouraging. A number of specific protein tyrosine phosphatases (PTPs) have been identified as candidate targets. Nevertheless, demonstration of the insulin-sensitizing efficacy of vanadyl sulphate in humans suggests that one or more PTPs may be viable drug targets. Recent results from genetic knockout of PTP-1B provide strong validation of this particular PTP as a potential target. Surprisingly, they also showed substantial resistance to diet-induced obesity.

Reducing excessive hepatic glucose production: Several enzymes that regulate rate-controlling steps in the gluconeogenic or glycogenolytic pathways are obvious molecular targets for therapeutic intervention (Fig: 1.4). Inhibitors of glycogen phosphorylase inhibit glucose output by decreasing hepatic glycogen

catabolism. Other relevant targets include fructose-1, 6-bisphosphatase which controls a rate-limiting step in gluconeogenesis and glucose-6-phosphatase which catalyses the final common step required for release of glucose from the liver, NEFA, non-essential fatty acids and PEP, phosphoenolpyruvate.

Antihyperglycemic isolates from Flavonoids represent the beneficial group of naturally occurring compounds with hypoglycemic potential. Intraperitonial administration of quercetin (1) to normal as well as streptozotocin-induced diabetic rats resulted in marked reduction in plasma glucose level of diabetic animals. Quercetin also suppressed the glucose level in diabetic rats in a glucose tolerance tests, reduced plasma cholesterol and triglycerides significantly and increased their hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets of the diabetic rats.

Quercetin 1, naringenin 2 and chrysin 3 significantly enhanced the insulin release from isolated rat islets of langerhans in presence of 20 mmol glucose/l. Effect of citrus bioflavonoids, hesperidin 4 and naringin 5 (Fig-1) on blood glucose level, hepatic glucose-regulating enzymes activities, hepatic glycogen concentration and plasma insulin levels were investigated in male C57BL/KsJ-db/db mice, type-II animal model.

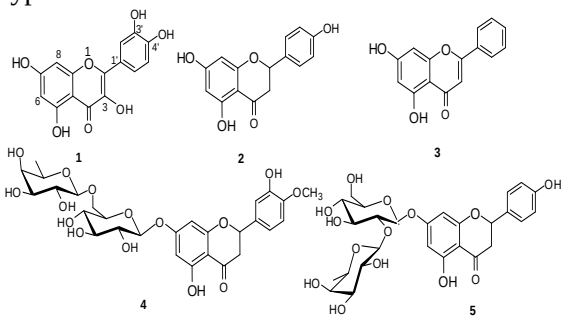

Fig-1: Represents the flavones based compound 1, 2, 3, 4 and 5.

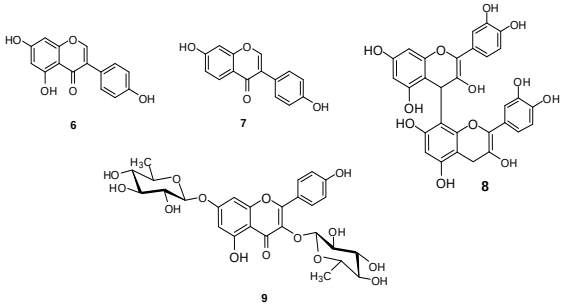

Fig-2: Represents the isoflavone based compounds 6, 7, 8 and 9.

One isoflavene viz, dehydroglyasperin D 10 and isoflavan 11, two 3arylcoumarins 12a, 12b and an isoflavanone 13 have been isolated as the PPAR-γ ligand-binding active ingredients of licorice (Glycyrrhiza uralensis roots). The isoprenyl group at C-6 in the ring-A and the C-2' hydroxyl group in the aromatic ring-C part in the isoflavan, isoflavene or arylcoumarin skeleton were found to be the structural requirements for PPAR-γ ligand-binding activity. Glycyrin 12b, one of the main PPAR-γ ligands of licorice, significantly decreased the blood glucose levels of genetically diabetic KK-Ay mice. (Fig-3)

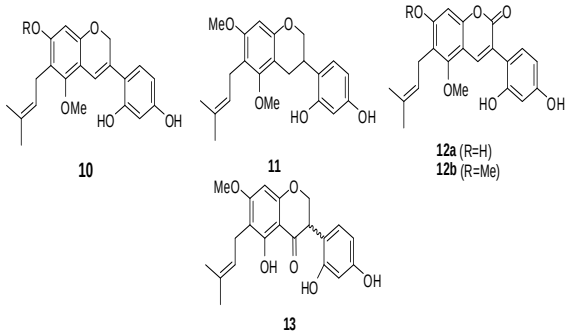

Fig-3: Dehydroglyasperin D **10**, isoflavan **11**, arylcoumarin **12a**, glycyrin **12b** and isoflavanone **13** as the PPAR-γ ligand-binding factors

Various active components like (−)-epicatechin 14, the benzofuranone, marsupsin 15, and the dihydro-β-hydroxychalcone, pterosupin 16 isolated from the bark and heartwood of Pterocarpus marsupium Roxb. were evaluated for their putative antihyperglycemic activity against streptozotocin-induced hyperglycemic rats and were found to possess blood sugar lowering activity. Aurone 17 is a most potent antidiabetic compound isolated from Uvaria hamiltonii. (Fig-4)

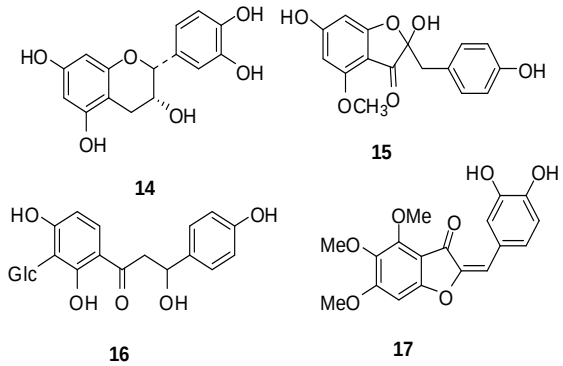

Fig-4: (−)-Epicatechin **14**, Marsupsin **15**, Pterosupin **16** and Aurone **17**

Triterpenoids:

Evaluation of in vivo anti-diabetic effects of cucurbitane triterpenoids from Momordica charantia revealed that the major compounds viz, 5β, 19-epoxy-3β,25-dihydroxycucurbita-6, 23-(E)-diene (18) and 3β,7β, 25-trihydroxycucurbita-5, 23-(E)-dien-19-al (19) have blood hypoglycemic effects in the diabetes-induced male ddY mice strain at 400 mg/kg. (Fig-5)

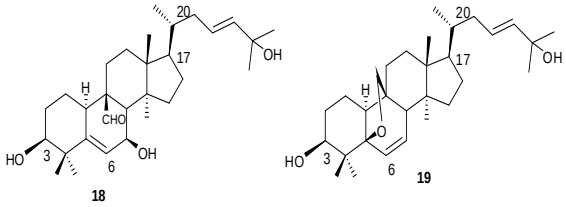

Fig-5: Cucurbitane triterpenoids **18** and **19**

Hypoglycemic activity guided fractionation together with chemical analysis led to the isolation of chloroform extract of 12-Ursene 20 and 23, 24-Dimethyl-24-ethyl-stigmast-25-ene (21) from the the dried stem of Agarista mexicana. (Fig-6)

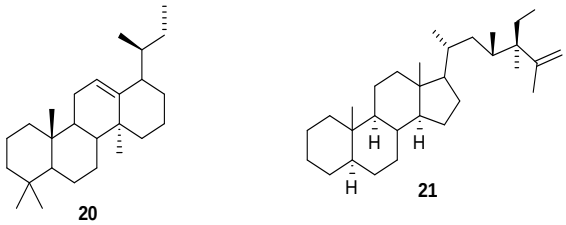

Fig-6: 12-Ursene **20** and 23, 24-dimethyl-24-ethyl-stigmast-25-ene (**21)**

Saponins:

Triterpenoid and steroidal glycosides collectively referred to as saponins are bioactive compounds present naturally in many plants and known to possess potent hypoglycemic activity. (Fig-7)

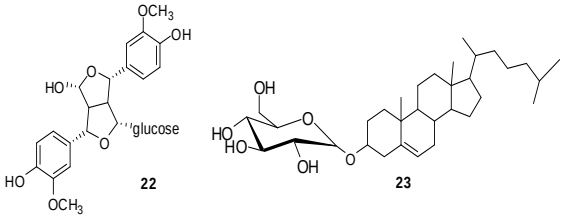

Fig-7: Charantin **22** and lactucaside **23**

Charantin 22 a steroidal saponin, obtained from Momordica charantia is known to have an insulin-like activity, responsible for its hypoglycemic effect. Charantin stimulates the release of insulin and blocks the formation of glucose in the bloodstream. Lactucaside 23 obtained from Lactuca indica were found to produce significant hypoglycemic activity.

Saponins with hypoglycemic activity 24-27 (Fig-8) were isolated from the methanolic extract of the leaves of Boussingaultia baselloides. Amongst these, Boussingoside A1 24 exhibited very strong antidiabetic activity in rats.

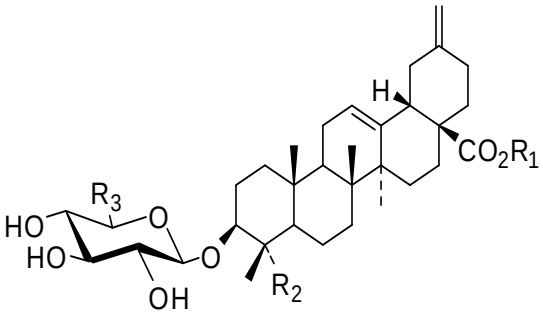

Fig-8: Boussingosides 24-27

Diterpenoids:

Andrographolide 28, a diterpenoid lactone, obtained from Andrographis paniculata was found to possess significant hypoglycemic activity. A diterpene, saudin 29 was isolated from the petroleum ether extract of Cluytia richardiana indica which showed significant antidiabetic activity (Euphorbiaceae) growing in Saudi Arabia.

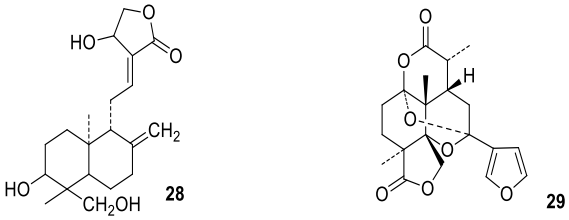

Fig-9: Andrographolide **28**, and saudin **29**

Sesquiterpene lactone: A sesquiterpene lactone, lactucain C 30 (Fig-10) was isolated from Lactuca.

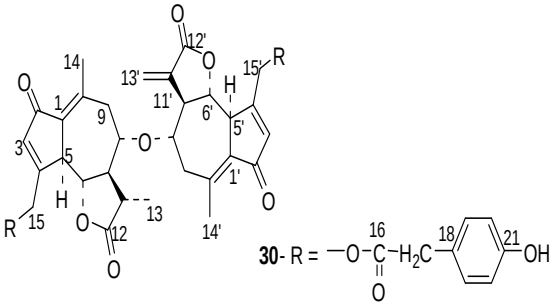

Fig-10: Lactucain

□-Carbolines:

Harmane 35, norharmane 36 and pinoline 37, (Fig-12) the □-carboline alkaloids were found to increase insulin secretion two to three-fold from isolated human islets of langerhans. Harmane and norharmane obtained from Tribulus terrestris L. may account for the hypoglycemic property of the plant. Harmane stimulates insulin secretion in a glucose-dependent manner. The results strongly substantiated the claim of □-carbolines as potent insulin secretagogues.

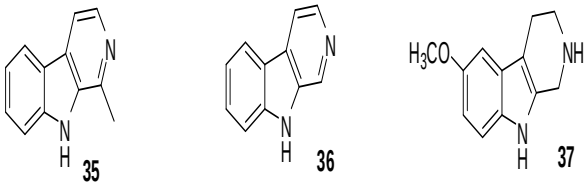

Fig-12: Harmane **35**, norharmane **36** and pinoline **37**

Bioassay-guided isolation and purification of hexane and ethyl acetate extract of Cabernet Sauvignon grape skin yielded antihyperglycemic active compounds which were identified as, sitosterol-6'-linolenoyl-3-O-□-D-glucopyranoside, oleanolic acid and oleanolic aldehyde.

Amino Acids:

FR225659 38 and four related compounds 39-42 (Fig-13) are gluconeogenesis inhibitors that consisted of an acyl-group and three abnormal amino acids. They were isolated from the culture broth of Helicomyces sp. and can be purified by absorptive resin and reverse-phase column chromatography. They were found to be potent inhibitors of gluconeogenesis in primary cultured rat hepatocytes and thus may be useful as anti-diabetic agents.

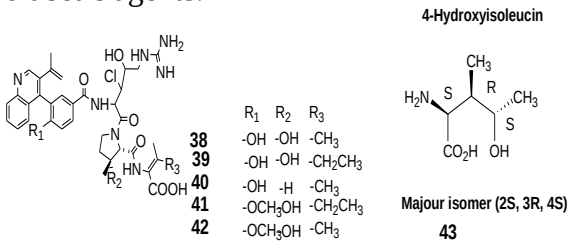

Fig-13: Amino Acids (**39-42)** as novel gluconeogenesis inhibitors, **43**

4-Hydroxyisoleucine 43 is a modified amino acid, not found in mammalian tissues, which is only present in some very specific plants, especially Trigonella species. This amino acid is mainly distributed in fenugreek Trigonella foenum graecum L. seeds.It stimulates glucose-induced insulin secretion in the micromolar concentration range through a direct effect on pancreatic-β cells in rats and humans.

Miscellaneous:

Allicin 44, (Fig-14) a sulphur compound isolated from garlic has resulted in pronounced hypoglycemia in mildly diabetic rabbits upon oral administration (0.25 mg/kg). Leporin B 45, (Fig-14) a demethylated analog of leporin A 46 was isolated from a taxonomically unidentified fungal strain to discover compounds with the ability to increase expression levels of the enzyme hexokinase II.

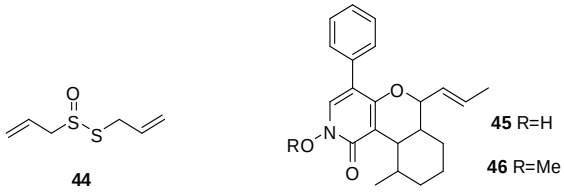

Fig-14: Allicin **44**, and leporin B **45**

Rat lens aldose reductase (RLAR) inhibitors 47-50 (Fig-15) from the fruiting bodies of Ganoderma applanatum were isolated, protocatechualdehyde 49 was the most potent RLAR inhibitor (IC50=0.7 μg/mL) equivalent to that of the positive control TMG (IC50 = 0.6 □g/ml).

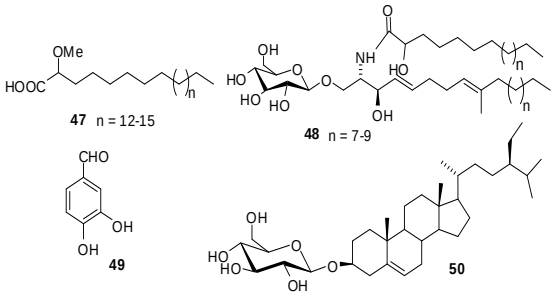

Fig-15: Rat lens aldose reductase (RLAR) inhibitors (**47-50**)

Two compounds viz, kodaistatin A 51 and kodaistatin C 52 (Fig-16) were isolated from cultures of Aspergillus terreus Thom. The kodaistatins are effective

inhibitors of the glucose-6-phosphate translocase component of the glucose-6-phosphatase system (EC 3.1-3.9), an enzyme system which is important for the control of blood glucose levels. The IC50 was 80 nM for kodaistatin A and 130 nM for kodaistatin C.

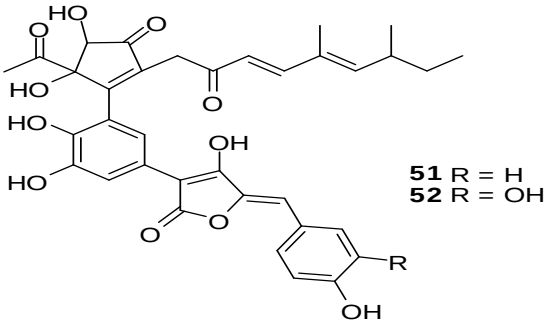

Fig-16: Kodaistatin A **51** and kodaistatin C **52** as glucose-6-phosphate translocase inhibitors

Conclusion

Type-II diabetes poses a lethal threat to mankind in the present health scenario. The more alarming situation has risen owing to the secondary complications associated with this silent killer. So, there is an urgent need for broad based drugs which can ameliorate this complex menace. Natural products have always been the inexhaustible source of new drugs from the time immemorial. Notwithstanding the significant headways in synthetic chemistry in the management of hyperglycemia, chemical entities emanating from the natural source still hold promise in alleviating the blood glucose levels and its concurrent ailments. More has been done but much has remained unexplored in the drug discovery paradigm of natural products attributed with therapeutic virtues. Some targets have been identified for the active principles but unless, their mechanism of action is not determined and clinical studies not performed, their potential as antihyperglycemics will remain unearthed. Moreover, the combination of plant based drugs and synthetic pharmaceuticals for correcting this metabolic error could pave way for cost-effective therapies. The scope of plant drugs lies in the rectifying the problem of adverse side effects generated by synthetic antidiabetic drugs, cost-effectiveness and minimal side-effects. The resurgence of natural products in the drug discovery and development may hold the key in the proper utilization of biodiversity for the management of hyperglycemia.

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