International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.13 | SPL 1 | Apr - Jun -2025

www.ijphr.com

ISSN: 2306-6091

DOI : https://doi.org/10.61096/ijphr.v13.(SPL1).2025.18-36

Review

A Review on Diabetes Mellitus: Type1 & Type2

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Published on: 03 May 2025

Published by:
DrSriram Publications

Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is broadly classified into Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM is an autoimmune condition leading to the destruction of pancreatic β-cells and subsequent insulin deficiency, typically manifesting in childhood or adolescence. In contrast, T2DM, the more prevalent form, is primarily associated with insulin resistance and relative insulin deficiency, commonly linked to genetic, lifestyle, and environmental factors. This review provides a comparative overview of T1DM and T2DM, including their etiology, pathophysiology, clinical features, diagnostic criteria, and management strategies. It also explores recent advances in treatment and highlights the importance of lifestyle modifications, early detection, and patient education in controlling disease progression and preventing complications. Understanding the distinctions and overlaps between T1DM and T2DM is essential for effective diagnosis, treatment, and research into potential cures.

Keywords: Diabetes, Glycemic index, Genetic, Diagnosis

INTRODUCTION

Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipidemia, hyper aminoacidemia, and hyperinsulinemia it leads to decrease in insulin, secretion and insulin action. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides, α glucosidase inhibitors and glinides. In developing countries products are expensive and not easily accessible [1]. Diabetes is a heterogeneous metabolic disorder characterized by altered carbohydrate, lipid, and protein metabolism which causes hyperglycemia resulting from insufficient insulin secretion, insulin action or both [2]. Diabetes is a serious global health issue, with type 2 diabetes mellitus (T2DM) accounting for approximately 90–95% of all cases [3]. The recent rapid increase in the prevalence of T2DM is in part due to an

ageing population but may also be attributed to an increase in the number of overweight and obese people. The prevalence of T2DM ranges from 1.2% to 14.6% in Asia, 4.6% to 40% in the Middle East, and 1.3% to 14.5 % in Iran [4]. Most of this increase is anticipated to affect the economically productive 45- to 64-year-old age segment in contrast with most developed countries, where the increase in diabetic patients will occur in those aged < 65 years [5].

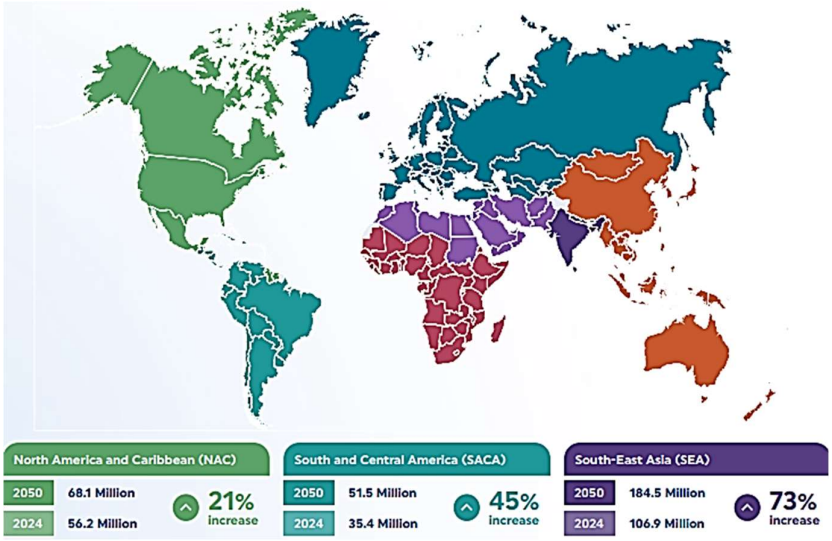

Fig 1: World wide data for Diabetic

Types of diabetes

Type 1 is insulin-dependent diabetes mellitus (IDDM), in which the body does not produce any insulin. It most often occurs in children and young adults. Type 1 diabetes accounts for 5–10% of diabetes.

Type 2 is noninsulin-dependent diabetes mellitus (NIDDM), in which the body does not produce enough, or improper use of secreted insulin is the most common form of the disease, accounting for 90–95% of diabetes. Type 2 diabetes is nearing epidemic proportions, due to an increased number of elderly people, and a greater prevalence of obesity and sedentary lifestyles.[6][7][8]

Basis of Diabetes Mellitus treatment

- Patient education concerning the disease
- Physical exercise
- Healthy Diet
- Hypoglycemic agents

As a very common chronic disease, diabetes is becoming the third “killer” of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases because of its high prevalence, morbidity and mortality. Therefore once diagnosed,[9][10] it is well regulated by means of various therapeutically effective drugs. Besides, the therapy based on chemotherapeutic agents, the present century has progressed towards naturopathy. Thus, medical plants have an ever emerging role to play in treatment or management of lifelong prolonging diseases like diabetes mellitus, especially in developing countries where resources are meager.[11][12] Diabetes mellitus alone is accompanied with several other diseases infecting healthy individuals. The treatment of each of such disease can be done by exploiting the herbal integrity of India. The plants in parts or as full can be used for curing any disorder related with diabetes mellitus. Moreover, in some cases extracts of plants are self capable of treating the related disorders such as polyuria, polydipsia, glucosuria, etc. along with curing the chronic disorders such as diabetes mellitus [13,14]

Some Common Sign and Symptoms

In diabetes mellitus, cells fails to metabolized glucose in the normal manner, effectively become starved [15]. The long-term effect of diabetes mellitus which includes progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and neuropathy with risk of foot ulcer, Charcot joint and features of autonomic dysfunctions and sexual dysfunction [24] People with diabetes are at increases risk of diseases[16][17]

Other, various symptoms are observed due to

i. Gluconeogenesis from amino acids and body protein, causing muscle wasting, tissue breakdown and further increases the blood glucose level.
ii. Gluconeogenesis from amino acids and body protein, causing muscle wasting, tissue breakdown and further increases the blood glucose level [18].

Causes of Diabetes Mellitus

Disturbances or abnormality in gluco-receptor of ß cell so that they respond to higher glucose concentration or relative ß cell deficiency. In either way, insulin secretion is impaired; may progress to ß cell failure [19]. The theory of principal in micro vascular disease leading to neural hypoxia, and the direct effects of hyperglycaemia on neuronal metabolism [20]

1. Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors, down regulation' of insulin receptors. Many hypersensitive and hyperinsulinaemic, but normal glycaemic and have associated dyslipideaemic, hyperuriaemiac, abdominal obesity. Thus there is relative insulin resistance, particularly the level of liver, muscle and fat. Hyperinsulinaemic has been implicated in causing angiopathy [21].
2. Excess of hyperglycaemia hormone (glucagon) etc. /obesity; causes relative insulin deficiency –the ß cells lag behind. Two theories have demonstrated abnormalities in nitric oxide metabolism, resulting in altered perineural blood flow and nerve damage.[22].
3. Other rare forms of diabetes mellitus are those due to specific genetic defects (type 3) like "maturity onset diabetes of young" (MODY) other endocrine disorders, pancreatectomy and gestational diabetes mellitus (GDM). [23]

Lifestyle modification for the management of both T1DM and T2DM

Food intake and exercise are the two main determinants of energy balance and are the cornerstones of DM management. Blood sugar levels must be regularly checked in people with T1DM. There are several ways to lower your risk of health issues, including creating a healthy food plan, getting regular exercise, and collaborating with the diabetes team to modify insulin therapy. Clinical investigations indicate that lifestyle modifications can lessen the risk of developing T2DM by delaying or preventing its onset (24,25).

The risk can be lowered by about 58% in just three years. Individuals with IGT, impaired fasting glucose (IFG), or an HbA1C level of 5.76-6.4% are strongly encouraged to obtain dietary and activity advice, according to the ADA. On the other hand, individuals who have already received a diabetes diagnosis should adhere to the dietary suggestions made by a qualified dietician (26). A certified dietician should provide nutrition counseling to those with diabetes. When combined with other elements of diabetes management, nutrition therapy can lower HbA1C by 1-2% and enhance clinical and metabolic results. For diabetic individuals who are also overweight (obese), a treatment objective should be reducing calorie consumption to reach and maintain a healthier body weight. The distribution of macronutrients is variable within advised ranges and will rely on the preferences and goals of each individual's therapy. There is a clinically significant improvement in glycemic control in individuals with T1DM and T2DM when low-glycemic-index carbohydrates are substituted for high-glycemic-index carbohydrates in mixed meals (27,28).

Aiming for moderate weight loss (≈7percentage of body weight) can help with blood glucose control, blood pressure and cholesterol management, and diabetes prevention and treatment. By controlling total calories and free carbohydrates in a well-balanced diet, weight loss is possible. Nonetheless, diabetic individuals who strictly follow a low-carb diet should be aware of potential adverse effects such as headaches, constipation, and hypoglycemia. To enhance glycemic control, other research has recommended consuming whole grains and complex dietary fiber. Research indicates that exercise, with or without a notable reduction in body weight, can enhance glycemic management (a reduction of 0.66% in the HbA1C level) and enhance patients' overall quality of life (29,30).

Adults ≥18 years of age should, to reap the greatest benefits, participate in moderate-intense activity for at least 150 min a week (such as walking at a 15–20 min mile pace) or 75 min a week of energetic physical activity (such as running, aerobics) spread over at least three days per week with no more than 2 days without exercise. For individuals who are at least 18 years old,1 h of physical activity each day is sufficient (31,32).

Additional lifestyle modifications that should be taken into account in the treatment plan for patients with diabetes include reducing sodium intake and moderate alcohol consumption (≤1 drink for women, ≤2 drinks for men), particularly in patients with comorbid conditions like hypertension, habitual tobacco use, and immunization deficiency (pneumococcal, hepatitis B, influenza, diphtheria, pertussis, tetanus, and tetanus). DM patients during should not consume alcohol while they are under treatment as it might cause potentially fatal hypoglycemia and coma, especially when fasting. Additionally, to effectively counteract the negative consequences of diabetes, patient education, counseling, and psychosocial support are crucial (33).

Current pharmacologic management of DM

Improving glucose control and lowering long-term consequences in T2DM are linked to early pharmacologic therapy beginning. Currently, it is treated using the following drug classes: insulin; biguanides; sulfonylureas; meglitinide derivatives; α-glucosidase inhibitors; thiazolidinediones; glucagon-like eptide–1-agonists; glucose-dependent insulinotropic polypeptide agonists; dipeptidyl peptidase iv inhibitors; selective sodium-glucose transporter–2 inhibitors are being employed as treatment regimens to manage DM across the globe. Each of these is covered in the manuscript's next section (33,34).

Insulin therapy for the management of T1DM and T2DM

For all T1DM patients, insulin is the main course of treatment. When first diagnosed, patients with T1DM usually need to start with several daily injections. Typically, one or more daily separate injections of intermediate- or long-acting insulin are administered in addition to 0 to 15 minutes of fast-acting insulin or rapid-acting insulin analog. One can use two or three premade insulin shots every day. The target HbA1c should be < 7.5% (< 58 mmol/mol) for all children having T1DM, including preschool-age children (34).

It is recommended to start insulin therapy in T2DM patients in the following situations: if they have an acute illness or surgery; are pregnant; have glucose toxicity; in case of severe kidney or liver failure are not able to reach their goals with oral antidiabetic drugs, or require flexible therapy. When HbA1c is = 7.5% (=58 mmol/mol), insulin is considered as a monotherapy or in combination with oral agents to help T2DM patients reach their glycemic goals. When HbA1c is =10% (= 86 mmol/mol), insulin is needed for treatment, if diet, exercise, and other antihyperglycemic agents have been properly implemented to their fullest potential (35,36)

Biguanides for the management of T2DM

The first-line treatment for T2DM blood sugar reduction has been metformin, a biguanide medication. The FDA has authorized this medication. This medication improves glycemic management by altering the liver's sensitivity to insulin. Nevertheless, there is little information available regarding the adverse effects of metformin, mostly from case reports. it's worth noting that metformin may harm a patient's ability to get a good night's sleep by causing atypical nightmares and, in rare instances, lactic acidosis (37).

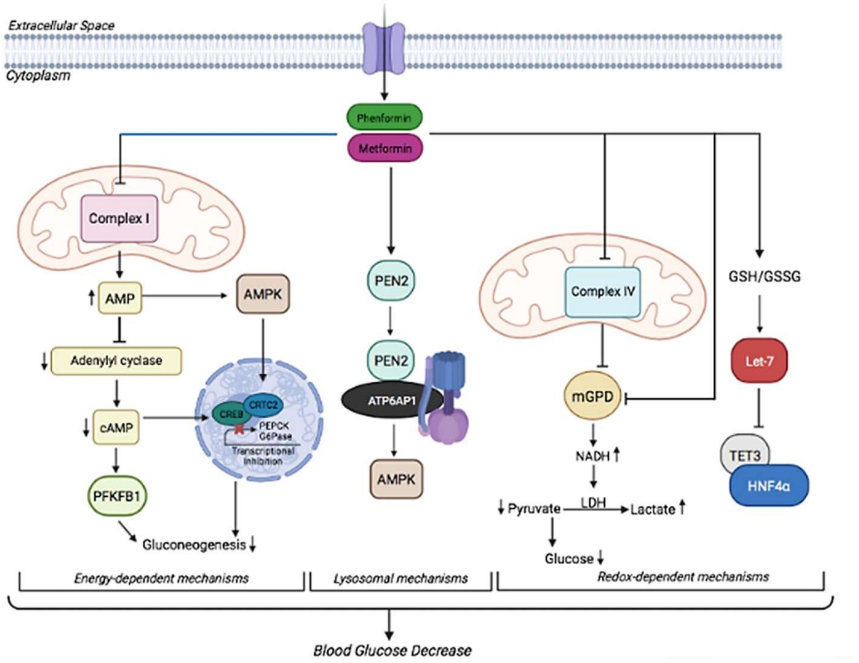

Fig 2: First line diabetes management

Sulfonylureas for the management of T2DM

People with T2DM who are not extremely obese are frequently treated with second-line medications known as sulfonylureas. T2DM has been treated with sulfonylureas since the advent of tolbutamide in the 1950s. They are divided into two groups: first-generation (acetohexamide, tolbutamide, chlorpropamide, and tolazamide) and second-generation (glibenclamide, ligmepiride, gliclazide, glipizide, and gliquidone agents). The fundamental distinction between both generations is that the agents in the second generation are substantially more powerful than those in the first. Sulfonylureas are secretagogues of insulin that enhance the quantity of insulin produced by pancreatic β-cells, therefore reducing plasma glucose levels (39,40).

Their mechanism action is by directly obstructing ATP-sensitive K+ channels on islet cells, which increases the generation of insulin. They depend on the presence of a sufficient number of cells with a sufficient functional reserve, but they remain effective until they accomplish their intended goals whether taken alone or in conjunction with other anti-hyperglycemic drugs. Sulfonylureas' primary acute side effect, is a higher incidence of hypoglycemia, particularly in elderly patients with impaired renal function, hepatic dysfunction, poor oral intake, calorie restriction, alcohol abuse, and other disorders (40.41)

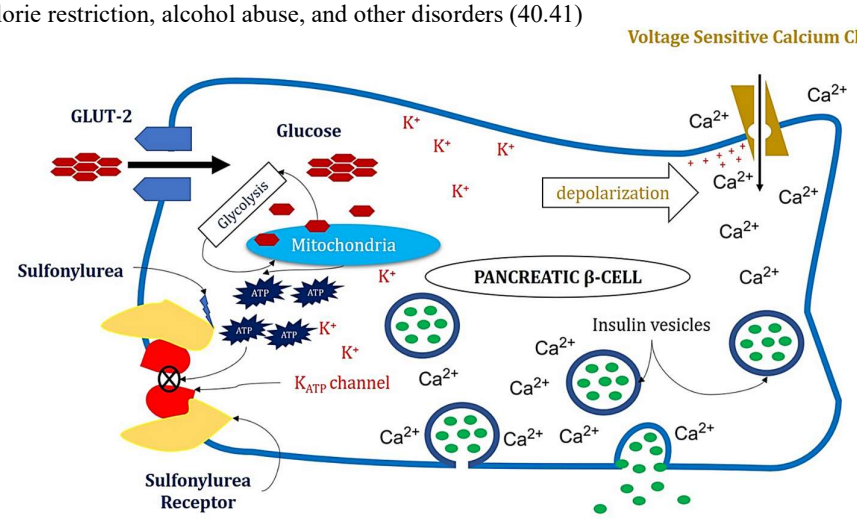

Fig 3: Sulfonylureas for the management of T2DM

Meglitinide derivatives for the management of T2DM

People with T2DM can better regulate their blood sugar levels by combining a healthy diet and exercise regimen with the insulin secretagogues repaglinide and nateglinide, generally known as "glinides." Meglitinide derivatives, as a monotherapy or in conjunction with metformin, can help adults with T2DM improve their glycemic control in addition to nutrition and exercise (42,43). The regulation of insulin synthesis by pancreatic β-cells involves cell membrane potential, which is determined by the inverse relationship between extracellular glucose levels and potassium channels' activity that are sensitive to adenosine triphosphate. Glucose transporters 2 transfer ($GLUT_2$) extracellular glucose into the cell. The cell uses and stores adenosine triphosphate (ATP) as energy after breaking down glucose as it enters the body. They increase the release of insulin by inhibiting ATP-sensitive potassium channels, which depolarize β-cells, and opening calcium channels, which let calcium in. Production of insulin is stimulated by elevated calcium in the cells levels (44,45).

α-glucosidase inhibitors (AGIs) for the management of T2DM

Among the oral AGIs used to treat diabetes are voglibose, miglitol, and acarbose. Inhibitors of α-glucosidase stop the small intestine from absorbing carbohydrates.[46][47] They obstruct the enzymes that change complicated, non-absorbable carbohydrates into simple, absorbable ones through competitive inhibition. These comprise the following enzymes: isomaltase, maltase, sucrase, and glucoamylase. They delay the absorption of carbohydrates, which lessens an increase in blood sugar levels after meals by about 3 mmol/l (reduced postprandial glucose).[48][49] The drug in this class that is most frequently used and researched is acarbose. α-amylase, sucrase, maltase, and dextranase are all inhibited by acarbose, however, it is more effective against glucoamylase. On the other hand, it does not affect the lactase β-glucosidase. These drugs are eliminated by feces, have a low absorption rate from the stomach, and have restricted bioavailability. Conversely, miglitol goes entirely through the kidneys and bypasses the stomach. While miglitol and voglibose do not undergo intestinal metabolism, acarbose does. For people who have a low glucose tolerance, in particular, they are therefore advantageous (63, 64). A doctor may recommend AGIs to a patient diagnosed with T2DM if they observe that their blood sugar tends to increase after meals. Moreover, the doctor might recommend adding an AGIs to their diabetic regimen if the patient is on medication for excessive blood sugar [50][51].

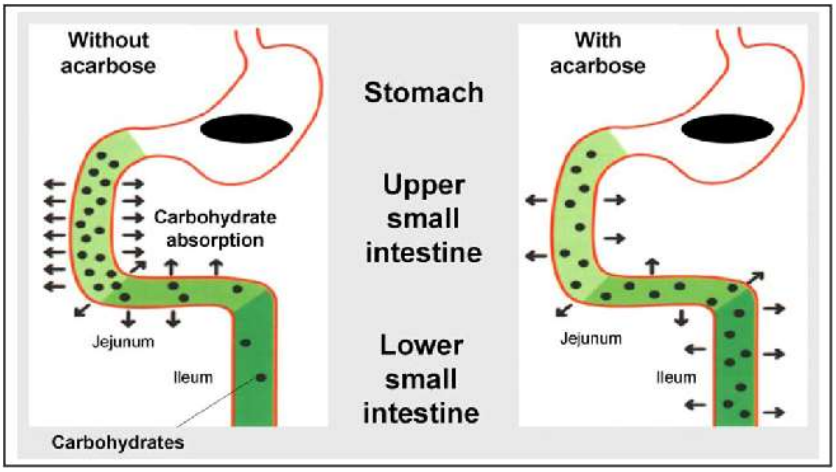

Fig 4: α-glucosidase inhibitors (AGIs) for the management of T2DM

Thiazolidinediones (TZDs) for the management of T2DM

TZDs (troglitazone, pioglitazone and rosiglitazone) are also known as glitazones work by sensitizing insulin to T2DM. Since their introduction in the late 1990s, TZDs have been utilized extensively because of their therapeutic benefits in treating insulin resistance and maintaining glycemic control. Troglitazone is the first TZDs drug that is approved by the FDA. However, it was taken off the market after 3 years as some patients' experienced serious liver toxicity. Right now, pioglitazone and rosiglitazone are the only TZDs medications available in the market for clinical use. TZDs are also recognized to possess anti-inflammatory and anti-cancer characteristics.[52][53]

There are no pharmacologic treatments that particularly treat insulin resistance other than TZDs. They are widely established that TZDs reduce the cardiovascular risk factors linked to insulin resistance. However, TZDs uses have been restricted because of worries about potential side effects and safety concerns. For instance, pioglitazone lowers myocardial infarctions (MI) and ischemic strokes, according to recent findings. The capacity of clinicians to choose patients who would experience few to no major side effects is enhanced by new information regarding TZDs-mediated congestive heart failure, bone fractures, and edema.[54]

Patients with T2DM benefit from TZDs because they lower glycemia, dyslipidemia, and insulinemia. By initiating the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ), they modify the expression of genes related to the homeostasis of glucose and lipids. Insulin sensitivity is increased when PPAR-γ is stimulated through many pathways. It does this through three different means: 1) it increases the expression of $GLUT_4$; 2) it controls the release of signaling molecules obtained from adipocytes that influence muscle's sensitivity to insulin; and 3) it induces apoptosis in adipose tissue, it causes the formation of adipocytes that are smaller and more flexible. Pancreatic β-cell activity is enhanced by TZDs by influencing the lipotoxicity of free-fatty- acids on islet cells of the pancreas. Recent approval for European commercial use has been granted to two TZDs: pioglitazone and rosiglitazone[55][56].

Peptidyl peptidase-4 inhibitor (DPP-4 inhibitors) for the management of T2DM

DPP-4 Inhibitors, also known as "gliptins" like sitaglibtin, saxagliptin, linagliptin, and alogliptin, progressively replace sulfonylureas to manage T2DM in numerous countries.[57][58] The three main advantages of these drugs are: 1) not associated with hypoglycemia or weight gain; 2) have a good safety profile; and; 3) used as an alternative to drugs such as metformin and sulfonylureas when fail. Their mechanism of action includes: increasing the mass and function of pancreatic β-cells; increasing insulin sensitivity in liver, muscle, and adipose tissue; decreasing dyslipidaemias; increasing fat oxidation and cholesterol efflux; lowering hepatic triglyceride synthase, decline *de novo* lipogenesis; postponing the time for stomach emptying and promoting satiety, have anti-inflammatory and antiatherogenic impacts, and improves endothelial function and reduces vascular stiffness (59). DPP-4 inhibitors are employed either as an add-on drug therapy when metformin (a biguanide), or sulfonylurea is inadequate or as monotherapy in individuals who should not be taking those medications or who are intolerant to them (60).

Glucagon-like peptide receptor agonist for the management of T2DM

Glucagon-like peptide-1 (GLP-1) receptor agonists also referred as incretin mimetics, or GLP-1 analogs like lixisenatide, liraglutide, albiglutide, exenatide, dulaglutide, and semaglutide are alarmingly used in combination with basal insulin to optimize glycemia, reduce weight, and optimize insulin dose requirements.

While exenatide is the first incretin mimetic licensed to be used in patients with T2DM, liraglutide is the preferred GLP-1 receptor agonist that can be used among those who have impaired renal function. Furthermore, high-dose liraglutide is FDA-approved as a pharmacologic treatment for obesity or can be prescribed to overweight patients with comorbidities. The benefits of this form of therapy to treat T2DM include 1) delayed gastric emptying, and 2) inhibiting the production of glucagon from pancreatic α- cells (61-63).

Sodium glucosinolate co-transporter 2 inhibitor for the management of T2DM

Sodium glucosinolate co-transporter 2 (SGLT-2) inhibitors (empagliflozin and dapagliflozin) are the most beneficial as an adjunct medication in addition to metformin in patients with a history of cardiovascular or renal disease that needs further HbA1c reduction. Due to their ability to lower the renal glucose threshold and raise urine glucose excretion, these medicines lessen hyperglycemia. The subsequent lowering of glucotoxicity enhances the sensitivity of tissue insulin and pancreatic β-cells to glucose. SGLT-2 inhibitors can also able to lower the body weight of individuals with obesity (64-66).

Novel and emerging therapeutic agents and/or targets for the management of both T1DM and T2DM

Current understanding of the pathophysiology of DM from the triumvirate of β cell failure to "ominous octet" has identified multiple pathogenic hotspots in the pathogenesis of DM [12]. Likewise, recognition of the "ominous octet" in the pathogenesis of DM has provided insight into the development of novel therapeutic agents against DM [66]. In a subsequent section of this manuscript, we have discussed the novel therapeutic agents against DM that can be used in the future for effective management of DM.

Stem Cell Therapy: An Emerging Arrow for Targeting Diabetes Mellitus

Various scientists working in stem cells established therapeutics pertaining to T1DM via the production of full-grown β cells originating from stem cells [67]. However, it becomes necessary to acquire the type and number of stem cells required for the treatment of the disease as it is an established fact that the pancreas does not have the capability of regeneration [68]. Embryonic stem cells (ESc) have the potential to differentiate into cells mimicking insulin secretagogue activity and various in vitro and in vivo studies have confirmed that the transformation of ESc into insulin-like cells results in the improvement of glucose uptake and metabolism [69,70]. Similarly, intravenous (IV) injection of embryonic-like stem cells (VSELs) in mice with pancreatic necrosis showed the potential to repair the damaged pancreas in diabetic patients [71] (fig,5).

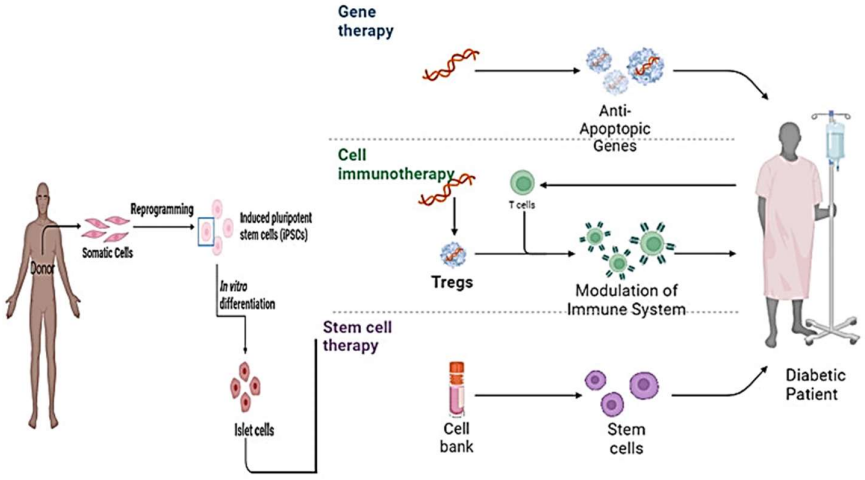

Fig 5: Stem Cell Therapy: An Emerging Arrow for Targeting Diabetes Mellitus

A smart biological system developed from mesenchymal stem cells isolated from the Wharton jelly component of the umbilical cord covered with immunoisolatory microcap- sules was observed to restore the β cell population of T1DM patients [72]. Furthermore, significant elevation of the C-peptide stratum was observed after implantation of mes- enchymal stem cells in six T2DM patients isolated from the umbilical cord. Consequently, postprandial stability in the serum glucose levels was noticed after 2 h [73]. To advance further, adiponectin, an adipocyte-secreted adipokine was observed to control the mobi- lization of bone marrow-derived mesenchymal stem cells (BMSCs). Adiponectin assisted in BMSC migration from the bone marrow into the circulation to regenerate bone by regu- lating stromal cell-derived factor (SDF)-1 in a mouse bone defect model and importantly lowered glucose levels and encouraged bone regeneration in

mice with diet-induced obe- sity [74]. Similarly, stem cells labeled with positron emission tomography (PET) tracer fluorine 18-fluorodeoxyglucose (F-FDG) to evaluate satisfactory administration methods for these cells in diabetic patients resulted in homing and retention of stem cells in the pancreas. Furthermore, infusion into the superior gastroduodenal artery (superior branch) was found to be the preferred route into the splenic artery as the former method resulted in better homing and retention of labeled stem cells [75]. The mesenchymal stromal cells with the insulin-secreting property isolated from the adipose tissue conjointly with the hematopoietic stem cells extracted from bone marrow, co-infused into the thymic portal circulation and subcutaneous tissue were found to regulate the hyperglycemia in TIDM patients [76]. Subsequent to the incorporation of human eyelid insulin-secreting stem cells (derivatives of adipose tissue), there was a lowering of serum glucose level in T2DM by increasing the insulin level in circulation [77]. The activity of the autoimmune mechanism underlying T1DM can be suppressed by immune ablation. Likewise, for immune ablation, 24 patients underwent transplantation of autologous hematopoietic stem cell transplantation (AHSCT) with a high dose of cyclophos- phamide and anti-thymocyte globulin. From these studies, it was found that AHSCT leads to a remission of T1DM with good glycemic control [78]. Furthermore, the possible risk factors identified for rejection of AHSCT therapy include levels of C-peptide (fasting), age and the levels of TNF-α [79]. In the later half of the 19th century, the attention of scientists was directed towards somatic cell-derived pluripotent stem cells (induced). The efficacy of somatic pluripotent cell lines/induced cell lines was reported as a healing technique for T1DM [80]. For instance, following the implantation of the altered epithelial cells isolated from the pancreas of non-obese diabetic mice within diabetic mice transformed precisely into insulin-producing cells with further significance in beta cell markers of the pancreas in addition to boosting the insulin release induced by glucose and potassium chloride [81]. To be more precise and accurate, Pancreatic stem cells were evaluated as therapeutic tools for amelioration of DM. In this direction, the intravenous injection of pancreatic stem cells in T1DM patients isolated from fetuses resulted in remarkable elevation of C-peptide levels after 3 months of intravenous injection of pancreatic stem cells [82].

Transdermal Drug Delivery System (TDDS)

The primary treatment regimen for the management of diabetes still remains the oral hypoglycemic drugs along with insulin injections [83]. Nevertheless, in the last 10 years, the TDDS has received considerable attention as an alternative regimen for the amelioration of diabetes due to its beneficial effects in comparison to the oral forms and injections, which are usually invasive along with being painful [84]. Other than carrying drugs such as insulin and metformin, the TDDS works by analyzing the metabolism via biosensing by evaluating metabolites in biological fluids like sweat. In this direction, ref. [85] designed a biosensor patch by incorporating a microneedle array (3D) for monitoring blood glucose levels. Furthermore, in vitro experiments indicated its stability in long-term use and the potential to check glucose levels even at extreme values. One of the limitations found in the experiment was that the sensitivity in detecting glucose levels decreased as glucose levels increased due to bio-fouling around the electrodes used. Hence, further improvement in the design is required to address this issue.

The development of effective transdermal systems faces challenges but also holds promise for improved patient compliance and therapeutic outcomes [86]. The techno- logical approaches adopted under TDDS include microneedle technology. Under this technology, tiny needles enhance drug delivery by creating microchannels hence improving the permeability of antidiabetic drugs. Likewise, nanoformulations have been used for TDDS of various anti-diabetic drugs, insulin sensitizers, and insulin. Furthermore, innovative techniques, which include iontophoresis and electroporation, utilize electric fields for the penetration of anti-diabetic drugs and insulin [87]. The advantages these approaches offer include non-invasiveness, steady and prolonged release, avoidance of first-pass metabolism, and reduced systemic side effects [30]. As research progresses, the translation of these technologies into clinically viable and widely accepted options remains an exciting avenue for improving diabetes care.

Nanotechnology

It is well understood that insulin injections used conventionally for TIDM and T2DM are accompanied by painful dispensing and infections which are associated with subse- quent low patient care [89]. Hence, to overcome these obstacles, the nanotarget perspective is undertaken, which is gaining tremendous popularity in the present era for being ac- curate, specific, efficacious, and favorable [90]. Henceforth, nanotechnology has been widely used for the management of DM due to the miniaturization of glucose sensors and closed-loop insulin delivery systems [91]. Accordingly, smart nanoparticles (NPs) as drug delivery systems contain glucose sensors, which help in sensing the glucose level in the body and accordingly help with insulin transportation. These bioengineered molecules contain microcapsules with pores that are small enough to permit the transit of insulin [92]. These nanoparticle formulations have been found to have greater drug bioavailability along with the fact that maximum drugs could be delivered at specific targets. However, their expandability and noxious nature can prove to be dangerous [93]. For

instance, a nanotechnology-based insulin delivery system offers precise targeting of pathogenic hotspots involved in the pathogenesis of DM at minimal doses, which improves the phar- macokinetics of insulin with reduced side effects [94]. Furthermore, quantum dots and mesoporous silica nanoparticles, have been employed to develop highly sensitive and selective glucose sensors [95]. Likewise, the integration of nanotechnology in smart insulin delivery systems allows for glucose-responsive insulin release [96]. Despite the significant strides in nanotechnology for diabetes management, challenges such as biocompatibility, long-term safety, and scalability must be addressed for clinical translation.

Novel Candidate Drugs for Management of DM

Fucoidan

The aquatic ecosystem is well known for the origin of nutraceuticals, cosmetics, and agro- nomic compounds (24). The various biologically active metabolites isolated from seaweeds (green algae, red algae, and brown algae) have been described to possess a wide range of pharmacological properties [97]. For instance, fucoidan obtained from sea cucumbers is a revolutionary biological sulfated polysaccharide [98,99]. Similarly, *Chorda filum*, *Fucus evanescens*, *Hizikia fusiforme*, *Sargassum stenophyllum*, *Laminaria hyperborean*, *Caulerpa racemosa*, *Analipus japonica*, *Fucus serratus*, *Padina gymnospora*, *Ascophyllum nodusum*, *Fucus vesiculosus*, and *Kjellmaniella crassifolia* have been explored for their fucoidan composition and have gained enormous interest for being agents of diabetes amelioration along with the amelioration of other metabolic diseases. Similarly, fucoidan isolated from the Fucus vesiculosus acts as a glucosidase inhibitor and thus plays a role as an anti-diabetic agent [100]. Additionally, fu- coidan has the capability of reducing diabetic retinopathy by the inhibition of VEGF (vascular endothelial growth factor) signaling [101]. In addition to this, in preclinical studies, fucoidan has been used for the management of diabetes via the alleviation of symptoms associated with the disease [102]. Fucoidan likely alleviates hyperglycemia by regulating acti- vated protein kinase (AMPK) signaling together with GLUT-4 action. Notably, Fuc-Pg, a fucoidan derived from the *Pearsonothuria graeei* (molecular weight -310 kDa) can be employed as a functional agent for the treatment of many metabolic disorders [103]. Moreover, Fuc-Pg was found to be responsible for the reduction of weight apart from decreasing hyperlipidemia and protecting the liver from steatosis in high-fat-diet-fed mice [104].

SGLT-2 (Sodium–Glucose Transporter-2) Inhibitors

Sodium–glucose transporter (SGLT-2) inhibitors, a distinct Na-glucose transporter ex- pressed by epithelia presented around renal proximal tubules comprise one futuristic ther- apeutic category for T2DM management. They are in greater numbers (around 90%) in the kidney tubular epithelium unlike SGLT-1 isoforms mostly found in intestines [105]. They act by barring the renal tubular glucose re-absorption along with showing an insulin discrete approach. Conceptually, these inhibitors could be utilized with the inclusion of other anti- diabetic drugs like insulin [106,107]. At Present, canagliflozin, dapagliflozin, and empagliflozin are commercially used in diabetic patients. Although this class of drugs has shown benefits, chronic outcomes of using this category of drugs still need to be evaluated [108].

Statin Therapy

Statins are considered novel therapeutic tools for the management and control of dia- betes. Statins are categorized under 3-hydroxy-3-methyl-glutaryl-coenzyme A, commonly known as HMG-CoA reductase inhibitor [109]. Statins are recognized for the filtering of LDL (low-density lipoprotein) and consequently diminishing their level in blood accompanied by the strengthening of blood vessels [110]. Henceforth, they offer the dual advantages of preventing cardiovascular disease (CVD), the most noticeable and prominent consequence of T2DM, and the amelioration of diabetic ketoacidosis. They are familiar lipid-lowering vehicles as they act on the cholesterol genesis pathway by transforming HMG-CoA into mevalonic acids. Importantly, a clinical trial was conducted on 6000 patients given statin therapy, and the study concluded that statin therapy acts on the lipolytic pathway and hence imparts a therapeutic effect by maintaining microvascular integrity, which prevents angiopathy in diabetic patients. However, chronic use was associated with myositis, hepatic disorders, and kidney problems [111]. Numerous clinical trials and observational studies have consistently demonstrated the anti-diabetic potential of statins. These drugs effectively lower low-density lipoprotein cholesterol (LDL-C) levels and reduce the risk of hyperglycemia-mediated cellular and subcellular damage. However, concerns have been raised regarding the association between statin therapy and the development of new-onset diabetes mellitus. Several large-scale studies, including the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and meta-analyses, have reported a modest increase in the risk of developing diabetes among statin users. Henceforth, decisions to initiate or continue statin therapy should involve a careful assessment of individual age, gender, family history, and baseline glucose metabolism. Based on these assumptions, finding an individualized approach

to statin therapy is crucial, taking into consideration the patient's diabetogenic risk factors. Henceforth, regular monitoring of blood glucose levels and glycated hemoglobin (HbA1c) is recommended, especially in patients with pre-existing risk factors for diabetes.

Quercetin Shielding against Diabetes

Quercetin [112] belongs to flavonoids and has been extracted from many fruits and vegetables like berries, onions, seeds, various nuts, barks, tea, flowers, leaves, and bras- sica vegetables [113]. Recently, pharmacological studies have shown that quercetin has biological properties relating to human health which encompasses protection against CVD, anti-allergic, anti-cancer, anti-ulcer, anti-inflammatory, anti-diabetic, and eye protection via avoidance of cataract formation [114]. Similarly, the role of quercetin as an antioxidant agent by inhibiting the enzyme xanthine oxidase is not clear. The greater hindrance in the utilization of quercetin is because of its lesser oral bioavailability, which is believed to be because of the presence of the sugar moiety of the molecule [115].

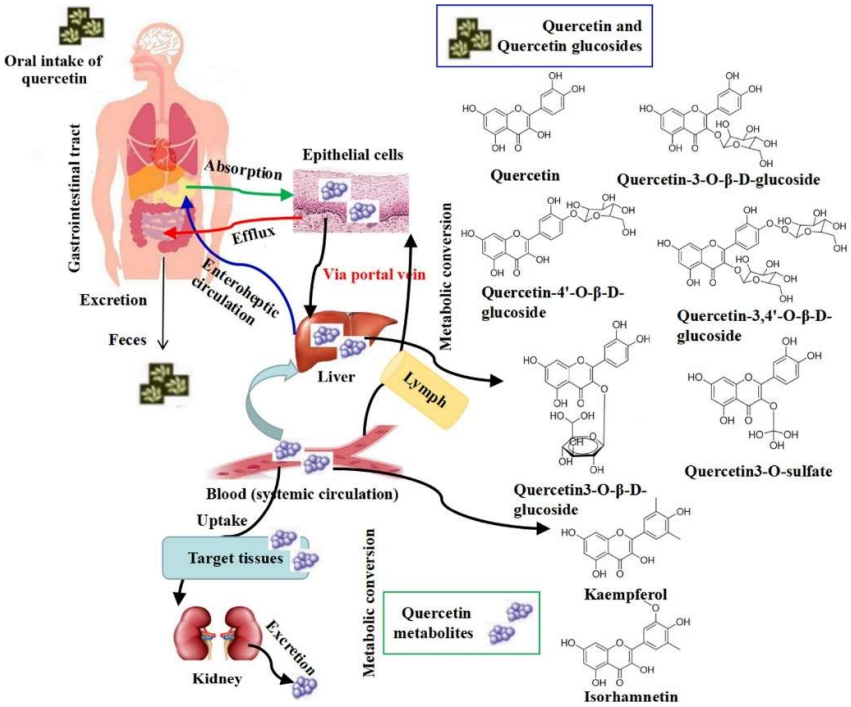

Fig 6: A The process of absorption, translocation and excretion of dietary quercetin in human body.

Quercetin has been progressively seen to decrease the complications of diabetes by acting on various signal pathways [116]. Moreover, administration of the different doses of quercetin orally in streptozotocin (STZ) and alloxan-induced diabetes rat models was capable of bringing down the blood glucose levels and glycosylated Hb (HbA1C) [117]. Following the oral administration of quercetin in a diabetic rat model, a significant decline in serum glucose levels was observed and the therapeutic mechanism was attributed to restoring the islet of Langerhans, boosting the insulin level in the serum along with stimulating the release of insulin. Furthermore, in T2DM mice models (C57BL/KsJ-db/db) and the high-fat diet-induced insulin resistance model [118], quercetin was observed to reduce the skeletal glucose uptake with subsequently influencing the insulin secretion (glucose-stimulated). It has been hypothesized that the hypoglycemic mechanism of quercetin might be attributed to GLUT (glucose transporter) expression or enhancing the insulin signal transduction via the upregulation of gene/protein expression (Figure 6) together with the phosphorylation of the insulin receptor or insulin receptor substrate. Similarly, quercetin showed a remedial approach against the significant complication of diabetes namely diabetic nephropathy through hypoglycemic, anti-inflammatory, and anti-oxidant characteristics [120].

Immunological Approach

Nowadays, immunological therapy has gained immense attraction for treating DM, especially T1DM. Usually, there are two immunological approaches namely non-antigen- specific and antigen-specific ones [121]. The most commonly used immunomodulatory agents gaining popularity include cyclosporine A, cytotoxic T cells, anti-CD3 cells, anti- thymocyte globulin, insulin, heat shock proteins, anti-TNF, glutamic acid decarboxylase, and mycophenolate mofetil. In addition to these, studies are being conducted on den- dritic cells, IL-4, IL-2, regulatory T cells, M2 macrophages, and the amalgam of IL-2 and rapamycin for evaluating their significance in amelioration of T1DM [122]. Among these agents, some of them have been evaluated for the management of T1DM in various animal.

Herbs and Compounds That Regulate Insulin Resistance

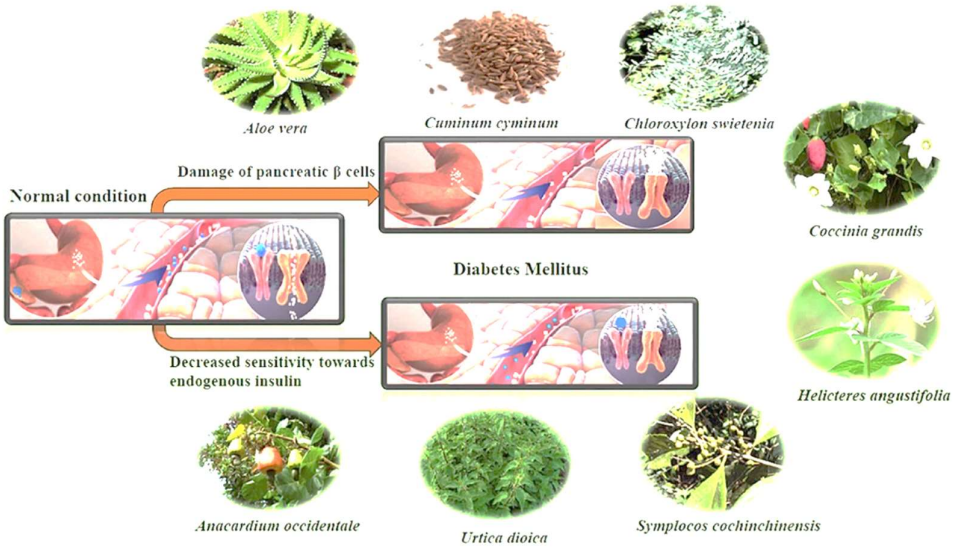

Fig 7: Role of herbs for regulating insulin resistance

Amorfrutins and Licorice

Licorice, the common name for the plants that comprise the genus *Glycyrrhiza*, is utilized as herbal medicine for a wide range of diseases. The ethanol extract of *G. uralensis* was found to reduce blood glucose, fat weight, and blood pressure in rodent models [124]. This extract also has PPAR-*γ* activity [125]. Further, amorfrutins isolated from the licorice, *G. foetida*, were found to bind to and activate peroxide proliferator-activated receptor-*γ* (PPAR-*γ*), a central player in glucose and lipid metabolism [126]. These compounds lowered blood glucose, fat weight, and dyslipidemia [127] indicating that licorice and its active amorfrutins exert their antidiabetic function via the PPAR-*γ* pathway.

Dioscorea* Polysaccharides and *Dioscorea

The rhizome of *Dioscorea* is used as a traditional Chinese medicine for asthma, abscesses, chronic diarrhea, and ulcers [128]. Several studies on rodent models of diabetes have reported that *Dioscorea* extract improves glycemic control and insulin resistance [128]. Further, *Dioscorea* extract reduced blood glucose in high fat diet-induced rats [128]. The antidiabetic mechanism of *Dioscorea* extract involves reduction of insulin resistance by diminution of the phosphorylation of ERK and pS6K and increase of the phosphorylation of Akt and glucose transporter 4 (Glut4) [129]. Another study demonstrated that *Dioscorea* polysaccharides reduced insulin resistance mediated by inflammatory cytokines as evidenced by the phosphorylation of insulin receptor substrate (IRS) and Akt [130].

Anthocyanins and Blueberry

Blueberry (*Vaccinium* spp.) was demonstrated to lower systolic and diastolic blood pressure and lipid oxidation and improve insulin resistance, diabetes, diabetic complications, and digestion [45, 129–132]. Notably, blueberries contain powerful antioxidants that can neutralize free radicals that cause neurodegenerative disease,

cardiovascular disease, and cancer [131]. Accordingly, phenolics and anthocyanins were proposed as active compounds for diabetes and insulin resistance [132].

One clinical study showed that obese or T2D patients consuming 22.5 g blueberry, twice a day for 6 weeks, reduced insulin resistance to a greater extent than those consuming a placebo. The data confirm the beneficial effect of blueberry on metabolic syndrome. However, the active compounds related to this claim need further investigation.

Astragalus Polysaccharides and Astragalus

The root of *Astragalus membranaceus* has long been used as a Chinese medicine and shows antioxidant, antidiabetic, antihypertensive, and immunomodulatory activities [133]. The extract of *A. membranaceus* was shown to treat diabetes and diabetic complications [134]. Moreover, treatment with *Astragalus* polysaccharides resulted in better glycemic control in diabetic rodents via an increase in insulin sensitivity [48–50]. The mode of action of *Astragalus* polysaccharides includes Akt activation and upregulation of Glut4 and inhibition of inflammation via the PTP1B/NFκB pathway [48, 50, 51].

Gastrodia elata

G. elata has been utilized as Chinese medicine for blood circulation and memory [135]. More recently, the extract of *G. elata* has been reported to improve insulin resistance [136]. Vanillin and 4-hydroxybenzaldehyde were proposed as the active compounds. Both compounds reduced insulin resistance through a decrease in fat accumulation in adipose tissues and an increase in fat oxidation and potentiation of leptin signaling in obese rats [137]. So far, no clinical study has been conducted in human diabetic patients.

Cinnamon

Both common cinnamon (*Cinnamomum verum* and *C. zeylanicum*) and cassia (*C. aromaticum*) have long been used as flavoring agents and in drinks and medicines worldwide [135]. Cinnamon has traditionally been used for rheumatism, wounds, diarrhea, headaches, and colds [136]. Recently, extensive studies have been performed on the action of cinnamon on diabetes and metabolic syndrome [135]. Cinnamon was shown to reduce blood glucose via reduction of insulin resistance and increase of hepatic glycogenesis [135, 137]. Cinnamon phenolics were proposed to be the active compounds in modulation of insulin signaling [53, 138, 139]. Moreover, cinnamaldehyde had antihyperglycemic and antihyperlipidemic effects on rodent models of diabetes [53]. This compound from cinnamon extract is thought of as a potential antidiabetic agent [139]. Unfortunately, the molecular target of cinnamon and cinnamaldehyde remains unclear.

Fenugreek

The seeds of fenugreek (*Trigonella foenum-graecum*) are used as a food supplement and also have a long history of medicinal use for labor induction, helping digestion and improving metabolism and health [34]. Animal studies have shown that extract of fenugreek seeds can lower blood glucose levels [140, 141]. Fenugreek is considered a promising agent for diabetes and its complications [34]. The glucose-lowering action of this plant involves reduction of insulin resistance [142]. Diosgenin, GII, galactomannan, trigoneosides, and 4-hydroxyisoleucine have been identified as the active antidiabetic compounds in fenugreek. However, little is known about the mechanisms of these compounds [55]. Among them, diosgenin was shown to reduce adipocyte differentiation and inflammation, implying its action in reduction of insulin resistance [54]. A clinical study indicated that fenugreek exerts hypoglycemic control via increasing insulin sensitivity [143].

Lychee

Lychee (*Litchi chinensis*) is an evergreen fruit tree. Its seeds are used as a Chinese herbal medicine for pain, gastrointestinal diseases, and others. Recently, lychee seed was reported to have antidiabetic activity in rats [56] and human patients [144]. Lychee seed extract exerts its action through reduction of insulin resistance [56]. In addition, oligonol from lychee fruit showed anti-oxidative activity and, thus, protected the liver and kidney in T2D animal models [57, 58].

Carica papaya* and *Pandanus amaryllifolius

The ethanol extracts of *P. amaryllifolius* and *C. papaya* reduced hyperglycemia in streptozotocin- (STZ-) treated mice [145]. Histological staining data showed that these extracts significantly induced the regeneration of the β cells as evidenced by reduced blood glucose level [146]. So far, no active components have been identified. However, the flavonoids, alkaloids, saponin, and tannin in both plants were speculated to be bioactive phytochemicals [59].

Therapeutic Application

The paradigm of antidiabetic therapy has shifted from monotherapy to combination therapy. So far, no antidiabetic agents, used alone or in combination, have been able to cure this disease in humans. A major challenge in the search for efficacious therapies is that the molecular basis of T2D etiology has not yet been fully deciphered.[147] Insulin resistance, β-cell function, glucose (re)absorption in the gut and kidney, and incretin production are the primary targets of current drugs. Compelling data on T2D treatment suggest that multiple targeting of the previous metabolic pathways is a plausible, albeit not yet fully developed approach to reversing T2D. Pharmacological interference of these targets with antidiabetic agents has undesirable side effects. [148] Due to the richness and complexity of the compounds in plants, herbal therapy has always been thought to act on multiple targets in the human body. Even one single compound can have multiple targets, as shown by the role of quercetin in inhibition of DPP-4, α-glucosidase, and other enzymes. Multiple targeting is a double-edged sword in diabetes therapies. [149][150] The multiple targets associated with antidiabetic herbal medicine make clinical trials complicated, but such an approach is more likely to lead to an eventual cure for T2D. In this review, the antidiabetic potential of the selected glucose-lowering herbs and their different mechanisms of action were summarized and discussed. The up-to-date information presented can be considered a cornerstone for further basic research and investigation into clinical applications of medicinal plants as T2D therapies

CONCULSION

Diabetes mellitus, both Type 1 and Type 2, remains a significant global health challenge with rising prevalence and serious long-term complications. While Type 1 diabetes is primarily an autoimmune disorder requiring lifelong insulin therapy, Type 2 diabetes is largely preventable and manageable through lifestyle modifications, pharmacotherapy, and early intervention. Despite their differences in pathophysiology, both types demand continuous monitoring, patient education, and a multidisciplinary approach for effective management. Advances in research, including genetic studies, new drug formulations, and emerging technologies like continuous glucose monitoring and artificial pancreas systems, offer hope for improved outcomes and quality of life for diabetic patients. Continued efforts in awareness, early diagnosis, and holistic care are essential in reducing the global burden of this chronic disease.

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