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Review Article
Promising Antidiabetic Drugs, Medicinal Plants and Herbs: An Update

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Abstract
Diabetes is a chronic endocrine disease with global prevalence and rising incidence. Diabetes represents a major health issue in all age groups in the present times owing to its multisystem involvement and serious complications. Despite drug development and therapeutic interventions, successful treatment of diabetes still remains a challenge and worldwide research is focused on these aspects. Conventional antidiabetic medicines include injectable insulins, sulfonylureas, biguanides, glucosidase inhibitors and glinides. New class include inhalable insulins, incretin mimetics, amylin analogues, gastric inhibitory polypeptide analogues, peroxisome proliferator activated receptors and dipeptidyl peptidase-4 inhibitors. From effectiveness of synthetic drugs, chemicals or hormones to issues of cost, availability and side effects, novelty in preparations to methods of administration, all fields are explored for better management of the disease. Medicinal plants with antidiabetic potential have been recent areas of research. Asteraceae, Araliaceae, Cucurbitaceae, Lamiaceae, Leguminoseae, Liliaceae, Moraceae and Rosaceae are the major antidiabetic plant families. The most active plants are Allium sativum, Gymnema sylvestre, Citrullus colocynthis, Trigonella foenum greacum, Momordica charantia and Ficus bengalensis. Their phytoconstituents have shown promising results in diabetes management; but need to be properly evaluated at molecular, physiological, pharmacological and toxicological levels for various prophylactic and therapeutic attributes, mechanisms of action, efficacy and safety before application in diabetes. The common phytoconstituents include polyphenols, flavonoids, terpenoids, tannins, alkaloids, saponins etc. Exploration of novel targets like glucagon-like peptide-1 (GLP-1), sodium-glucose co-transporter 2 (SGLT-2) and dipeptidyl peptidase 4 (DPP-4) for antidiabetic drugs and medicinal plants with emphasis on site specific effectiveness and overcoming problems of resistance, side effects, prolonged usage and high cost, are being investigated for future research.

Key words: Antidiabetic, drugs, medicinal plants

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INTRODUCTION

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar or glucose) or when the body cannot effectively use the insulin it produces[1]. It is a worldwide health related issue of the present times. Both the number of cases and the prevalence of diabetes have been steadily increased over the past few decades. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980[1]. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7-8.5% in the adult population. Prevalence is increasing more in poor countries than rich ones. Diabetes has caused 1.5 million deaths in 2012 with hyperglycemia and resulted in additional 2.2 million deaths, by increasing the risks of cardiovascular and other diseases. The majority of people with diabetes are affected by type 2 diabetes (where the body cannot properly use the insulin it produces) than the type 1 (were insulin is deficient). This used to occur nearly entirely among adults, but now occurs in children too[1,2]. Though this disease is of endocrine nature but complications involve cardiovascular, renal, nervous, immune system and other systems of the body resulting in severity of disease[1,3,4].

Diabetes Mellitus (DM) has become the most common endocrine dysfunction in the world caused by defect in insulin dynamics[1]. By year 2030 more than 439 million people are believed to be affected by diabetes[1,5]. India is one of the epicentres of the global DM pandemic[2]. Additionally, diabetes is a fast growing potential epidemic syndrome in India with more than 62 million diabetic patients currently diagnosed every year[6]. It is predicted that by the year 2030 such cases may increase up to 79.4 million, posing potential risk imposed by diabetes[4,7].

Keeping in view the alarming rise in number of cases and increase in prevalence of diabetes besides its complications and mortalities, the disease needs to be addressed both prophylactically and therapeutically. However type 1diabetes could be treated by insulin, type 2 diabetes requires a combination of therapies[1,8] and recent advances are being made for devising effective prophylactic and therapeutic protocol for management of both types[8-11]. The costs of caring for diabetes and its related complications are staggering with conventional therapeutics being expensive, prone to side effects and rarely being available in most of the developing or under developed countries[1,12,13].

Drugs, both chemicals and hormones are being used for treatment of diabetes[14,15]. Despite their effectiveness there are concerns regarding side effects and in middle and low income countries cost and availability also matters[1,16-18]. In the present era of emerging drug resistance and flaring up of several infectious as well as non-infectious diseases including general health problems in humans, herbal medicines are gaining high momentum and attention of worldwide researchers for exploring their multiple beneficial health applications and to be used as promising alternative and complementary options for prevention and treatment purposes both in humans and animals[19-24].

Application of medicinal plants for management of diabetes has been reviewed[25-35]. Medicinal plants are being used for both prophylactic and therapeutic management of diabetes[11,28,36,31]. Prophylactic action may be attributed to healthy organs and their cellular tissue especially beta cells of pancreas, hepatic tissue and preventive action on diabetic inducers[11,28,36,37]. Therapeutic action may be due to curative action on affected tissue of pancreas, liver and organs related to diabetes[37-41]. Presence of different phytoconstituents in these plants is responsible for these actions. Phenolics, flavonoids, terpenoids, alkaloids, anthraquinones, tannins, saponins, minerals etc may be some of the essential constituents in these plants which contribute to their antidiabetic potential[11,37,42-49]. However detailed molecular evaluation of phytoconstituents from medicinal plants with antidiabetic potential is essential for safe and effective use.

Antidiabetic drugs: Antidiabetic drugs have been used for treatment of diabetes since the reporting of this disease and even today and research is going on for developing newer drugs. These drugs are highly effective but are costly and are believed to be associated with serious side effects. Also, availability in developing or underdeveloped countries is either lacking or negligible. Insulin constitute one of the main antidiabetic treatment protocols. They can be natural from humans or animals or synthetic prepared in vitro. Though insulin is essential for treatment of type 1 diabetes but type 2 diabetes requires such type of drugs which help in insulin secretion or lower glucose levels. Commonly used antidiabetic drugs are those belong to sulfonylureas, biguanides, glucosidase inhibitors and glinides which have hypoglycemic effect. They are used as monotherapy or in combination to achieve better glycemic regulation. However lifelong requirement pose threat of side effects.

Antidiabetic drugs can be injectable or oral based on method of administration.

Injectable antidiabetic drugs

Insulin: Insulin, a pancreatic hormone produced by beta cells of Islets of Langerhans has been used for treatment of diabetes[50-52]. Usually it is injectable form[53]. It can be very rapid acting insulins (30 min absorption, 1-2 h peak action),

rapid-acting (short-acting) insulins (30-60 min absorption, 6-8 h peak action), intermediate-acting insulins (3-4 h absorption, 7-9 h peak action), long-acting insulins (10-12 h absorption, 16-18 h peak action) or premixed insulins[39-42,52,54].

Injectable insulins have many short comings hence novel insulin formulations and innovative insulin delivery methods, such as oral or inhaled insulin, have been developed with the aim to reduce insulin-associated hypoglycaemia, lower intraindividual pharmacokinetic and pharmacodynamic variability and improve imitation of physiological insulin release[55,56]. Insulin being a peptide hormone gets destroyed in stomach by gastric acid when taken orally. Intradermal absorption of insulin cannot mimic physiological insulin secretion hence it is not reliable. Subcutaneous route is preferred due to the ease of self-administration rather than other parenteral routes like intradermal, intramuscular and intravenous which are not suitable for self-administration daily. Despite the easy use of subcutaneous route, it causes pain at injection site, lipodystrophy, noncompliance by the patient, etc[57]. Therefore newer methods of insulin delivery aim to deliver insulin with minimal invasiveness in an accurate and precise manner and to reduce patient burden[57]. New Insulin Agents are recent class of insulins that are inhalable rather than injectable[52]. Technosphere insulin human (Afrezza) is a recombinant regular human insulin inhalation powder approved by the FDA in June 2014 for the treatment of type 1 and type 2 DM. When the insulin is inhaled through the device, the powder is aerosolized and delivered to the lung. Afrezza should be administered at each mealtime and is touted as an alternative to injectable short-acting insulin[58,59]. Other insulin preparations are oral, nasal, buccal, transdermal, intraperitoneal, ocular and rectal. Each route and delivery method has its own potential advantages and disadvantages. However, if successful, alternative routes of administration could revolutionize the treatment of DM and help improve patients' quality of life[52].

Oral antidiabetic drugs: These include insulin secretagogues which help in insulin secretion from beta cells of pancreas like sulfonylureas, meglinitides and peptide analogues (incretin) and glucose uptakers or metabolisers like alpha-glucosidase, thiazolidinediones (glitazones) inhibitors (miglitol and acarbose) and biguanides[39,60-64] which either help in glucose uptake and utilization in cellular tissues or metabolism of glucose.

Recent approaches in drug discovery have contributed to the development of new class of therapeutics like incretin mimetics, amylin analogues, gastric inhibitory polypeptide (GIP) analogs, peroxisome proliferator activated receptors and dipeptidyl peptidase-4 inhibitor (DPP-4) as targets for potential drugs in diabetes treatment[41]. These will either help in stimulation of insulin secretion through glucagon-like peptide (GLP) analogues like Exenatide and Liraglutide[65,66], compensate for beta cell defects (insulin injections), DPP-4 inhibition by Sitagliptin and increased islet survival[67,68] and islet cell regeneration through islet neogenesis associated protein (INGAP) peptide therapy aiming at islet cell regeneration among others[69].

From conventional approach of curing diabetes at pancreatic level, current research also focuses on extrapancreatic or indirect pancreatic approaches involving organs or mechanisms that ameliorate diabetic alterations. Sodium Glucose Cotransporter-2 Inhibitors (SGLT-2) are proteins found in the proximal convoluted tubule of the kidneys and are responsible for reabsorbing approximately 90% of the glucose that is filtered through the kidneys[70] thus their inhibitors promote glucose excretion through urine[71].

Glucagon-Like Peptide-1 hormones like incretin (GLP-1) are secreted by cells in the small intestine during an oral nutrient load. In the presence of hyperglycemia, GLP-1 causes the release of insulin from the pancreas, shuts down glucagon secretion, slows down gastric emptying and acts on the hypothalamus to increase satiety[71]. Currently, 4 GLP-1 agents are approved by the FDA which are exenatide, albiglutide, dulaglutide and liraglutide.

Dipeptidyl peptidase-4 inhibitors (DPP-4) are anti-hyperglycemic agents indicated for improving glycemic control in patients with type-2 diabetes. They slow the inactivation and degradation of GLP-1. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying and decreases blood glucose levels[72].

Other advanced approaches for diabetes treatment include stem cell therapy[73], nanotechnology[74,37] and gene therapy[75]. The issues with antidiabetic drugs are high cost, less availability, prolonged requirement and side effects. This has rendered effectiveness of these drugs inconvincible. Common side effects of antidiabetic drugs are related to gastrointestinal, cardiovascular, urinary, hematopoietic, nervous system or skin. Sulfonylureas cause low blood sugar, upset stomach, skin rash or itching and weight gain. Biguanides/metformin cause sickness with alcohol, kidney complications, upset stomach, tiredness, dizziness, metal taste and clotting defects. While, alpha-glucosidase inhibitors cause gas bloating and diarrhea[76,77]. However they are still being used world over and their demand is huge. Such side effects

pose threat on population health so attention is being paid towards natural remedies and traditional methods of treatment with emphasis on utilization of medicinal plants.

Antidiabetic medicinal plants: Concerns regarding efficacy and safety of oral hypoglycemic agents[78], cost and availability of insulin[79] have prompted research in alternative fields. Medicinal plants have a great promise in the management of diabetes due to presence of many active components, lack of side effects, cheapness and ease of availability, safe and efficacious nature. These medicinal plants may contain phytoconstituents that have antidiabetic effect. These phytoconstituents include phenolics, flavonoids, terpenoids, alkaloids, coumarins, anthraquinones, tannins, saponins, carbohydrates, cardiac glycosides and minerals which have proven antidiabetic activity through different mechanism of actions like insulin like action or secretion, regeneration of beta cells of the islets of Langerhans, hypoglycemic effect, hepato-pancreatic protective effect, reduced glucose absorption, favouring peripheral glucose utilization as well as glycogenolysis or reducing carbohydrate absorption, inhibition of aldose reductase activity, reduction of lactic dehydrogenase and γ-glutamyl transpeptidase, inhibition glycogen-metabolizing enzymes, increasing glyoxalase 1 activity in liver, increasing the creatine kinase levels in tissues, inhibition of glucose-6-phosphate system[11,39,42-49,80] besides being antioxidants and immunomodulators[11,37].

Phenolic compounds have also shown insulin mimetic property[81], biomolecule protector action[82] besides being antidiabetic[83]. Flavonoids have antidiabetic potential[84,85]. They improve glucose metabolism, lipid profile, regulating the hormones and enzymes in human body, further protecting human being from diseases like obesity, diabetes and their complications[86]. They are also having antioxidant, immunomodulatory and hepato-pancreatic protective action[11,37]. Terpenoids and saponins have antihyperglycemic activity, help in uptake of the glucose in the muscle and the inhibition of the glucose absorption in the gastrointestinal tract, insulin release activity, antioxidant activity and insulin mimetic property[46,81,87,88]. Alkaloids have antidiabetic and antioxidant property[45]. Anthraquinones are antidiabetic, antioxidant and alpha glucosidase inhibitory action[89]. They suppress chemokine-mediated leukocyte migration towards pancreatic islets leading to a decline in autoimmune diabetes development[90]. Similarly various phytoconstituents from medicinal plants like tannins, glycosides, minerals, have been evaluated for antidiabetic potential through different mechanisms like hypoglycemic effect, insulin release activity, hepato-pancreatic protective action, glucose uptake and utilization in muscles, inhibition of glucose absorption in intestines, antioxidant and immunomodulatory effect[11,37,39,42-49,91,92]. Additionally, phytoconstituents isolated from medicinal plants has been used by pharmaceutical companies for development of new drugs.

Though the medicinal plants have been beneficial in management of diabetes but the issues related to safety and efficacy need to be evaluated as there are reports of toxicity and inefficacy of some antidiabetic plants[93-97]. Some antidiabetic plants may contain phyconstituents that pose health risks and may affect vital organs like liver and kidney[37,98] or cause cardiovascular and neurological disturbance[99,100]. The list of antidiabetic plants is presented in Table 1.

Targets of antidiabetics: Different targets have been used for ameliorating diabetes by antidiabetic drugs or medicinal plants[32,163,164] as shown in Fig. 1. Some focused on reducing blood sugar while others at increasing insulin secretion from beta cells of islets of Langerhans[165,166]. Initially antidiabetic medication focused primarily on pancreatic approach with emphasis either on insulin secretion or glucose reduction. Then approaches through glucose uptake and metabolism were explored. Presently besides conventional approaches extrapancreatic and indirect pancreatic approaches are being investigated[71,164,167,168]. Various novel targets have been identified and recently various therapeutic leads successfully completed their different phases of clinical trials such as GLP-1 agonist, DPP-IV inhibitors, SGLT2 inhibitors and are going to be the next generation therapy for management of diabetes[32,71,164].

New and emerging classes of antidiabetic drugs, including the SGLT-2 inhibitors, 11 β-hydroxysteroid dehydrogenase type 1 inhibitors, glycogen phosphorylase inhibitors; protein tyrosine phosphatase 1B inhibitors, G protein-coupled receptor agonists and glucokinase activators hold the potential of providing benefit of glucose lowering, weight reduction, low hypoglycemia risk, improve insulin sensitivity, pancreatic β cell preservation and oral formulation availability. However, further studies are needed to evaluate their safety profile, cardiovascular effects and efficacy durability in order to determine their role in type 2 diabetes management[169].

Impairment in insulin secretion from beta cells, increased glucose production in liver and decreased utilization of glucose in peripheral tissues are the main defects responsible for the development and progression of DM and further pathophysiology involves adipocyte insulin resistance (increased lipolysis), reduced incretin secretion/sensitivity, increased glucagon secretion, enhanced renal glucose

Table 1: Antidiabetic medicinal plants

Plants	Plant part	References
Nigella glandulifera Freyn (*Ranunculaceae*)	Seeds	Tang *et al.*[101]
Salvia officinalis (Sage)	Leaf	Kianbakht *et al.*[102]
Chamaemelum nobile	Aerial parts	Eddouks *et al.*[103]
Rheum turkestanicum Janischew	Root	Hosseini *et al.*[104]
Calotropis procera	Leaf	Kazeem *et al.*[105]
Rauwolfia serpentina	Root	Azmi and Qureshi[106]
java plum (*Syzygium cumini*)	Fruit	Yousaf *et al.*[107]
Bitter gourd (*M. charantia*)	Fruit	Yousaf *et al.*[107]
Morus alba	Fruit	Jiao *et al.*[108]
Ficus carica	Leaves	Irudayaraj *et al.*[109]
Morus alba L.	Leaf	Gryn-Rynko *et al.*[110]
Averrhoa bilimbi	Fruits	Kurup and Mini[111]
Aframomum melegueta	Fruit	Mohammed *et al.*[112]
Euphorbia denticulata Lam.	aerial parts	Zengin *et al.*[113]
Syzygium densiflorum	Fruit	Krishnasamy *et al.*[114]
Eriobotrya japonica Lindl.	Leaf	Liu *et al.*[115]
Calotropis procera	Leaf	Kazeem *et al.*[105]
Rose rugosa	Whole plant	Liu *et al.*[116]
Nigella sativa	seed	Kooti *et al.*[117]
Adenanthera pavonina	leaf	Wickramaratne *et al.*[118]
Prunella vulgaris L. (*Lamiaceae*)	spikes	Raafat *et al.*[119]
Solanum trilobatum	Leaf	Ahmed *et al.*[120]
Syzygium cumini	Fruit	Yousaf *et al.*[107]
Momordica charantia	Fruits	Yousaf *et al.*[107], Habicht *et al.*[121]
Thymus serpyllum	Whole plant	Alamgeer *et al.*[122]
Turnera subulata	Leaf	Souza *et al.*[123]
Moringa oleifera	Leaf	Nunthanawanich *et al.*[124]
Pomegranate	Seed	Mollazadeh *et al.*[125]
Juglans regia L.	Leaves	Hosseini *et al.*[126]
Morinda lucida	Stem bark	Domekouo *et al.*[127]
Coreopsis tinctoria	Flower	Cai *et al.*[128]
Zanthoxylum chalybeum	Root bark	Agwaya *et al.*[129]
Balanites aegyptiaca	Fruit	Abou Khalil *et al.*[130]
Petroselinum sativum	Leaves	Abou Khalil *et al.*[130]
Fenugreek	Seeds	Jiang *et al.*[131]
Tamarix gallica	Aerial parts	Ben Hmidene *et al.*[132]
Euonymus alatus	Leaves	Zhai *et al.*[133]
Boswellia serrata	Gum resin	Mehrzadi *et al.*[134]
Phellinus linteus	Fruit	Yamac *et al.*[135]
Parkia roxburghii	Pod	Sheikh *et al.*[136]
Chinese bayberry (*Morella rubra* Sieb. et Zucc.)	Fruit	Yan *et al.*[137]
Prosopis farcta	Fruit	Dashtban *et al.*[138]
Cassia fistula	Stem bark	Agnihotri and Singh[139]
Tamarindus indica	Stem bark	Agnihotri and Singh[139]
Andrographis paniculata	Leaf	Taher *et al.*[140]
Garcinia mangostana	Fruit	Akhtar *et al.*[141]
Azadirachta indica (Neem)	Leaf	Satyanarayana *et al.*[142]
Aristolochia ringens	Root	Sulyman *et al.*[143]
Curcuma longa	Seed	Khaliq *et al.*[144]
Piper nigrum	Seed	Khaliq *et al.*[144]
Phoenix dactylifera	Seed	Khaliq *et al.*[144]
Hypoxis hemerocallidea	Stem	Oguntibeju *et al.*[145]
Aframomum melegueta	Fruit	Mohammed *et al.*[146]
Swietenia macrophylla	Seed	Kalpana and Pugalendi[147]
Grewia asiatica	Fruit	Khattab *et al.*[148]
Toddalia asiatica	Leaf	Irudayaraj *et al.*[109]
Swertia corymbosa	Aerial parts	Mahendran *et al.*[149]
Diospyros peregrina	Fruit	Dewanjee *et al.*[150]

Table 1: Continue

Plants	Plant part	References
Phyllanthus emblica	Fruits	D'Souza *et al.*[151]
Aegle marmelos	Leaf	Narendhirakannan *et al.*[152]
Rosa canina	Fruit	Taghizadeh *et al.*[153]
Medicago sativa	Sprouts	Seida *et al.*[154]
Calendula officinalis	Aerial parts	Moradkhani *et al.*[155]
Lonicera japonica	Stem	Han *et al.*[156]
Semecarpus anacardium	Stem bark	Ali *et al.*[157]
Actinidia kolomikta	Root	Hu *et al.*[158]
Allium cepa	Stem	Akash *et al.*[159]
Butea monosperma	Leaves	Sharma and Garg[160]
Zingiber officinale	Rhizome	Ilkhanizadeh *et al.*[161]
Ruta montana	Aerial part	Farid *et al.*[162]

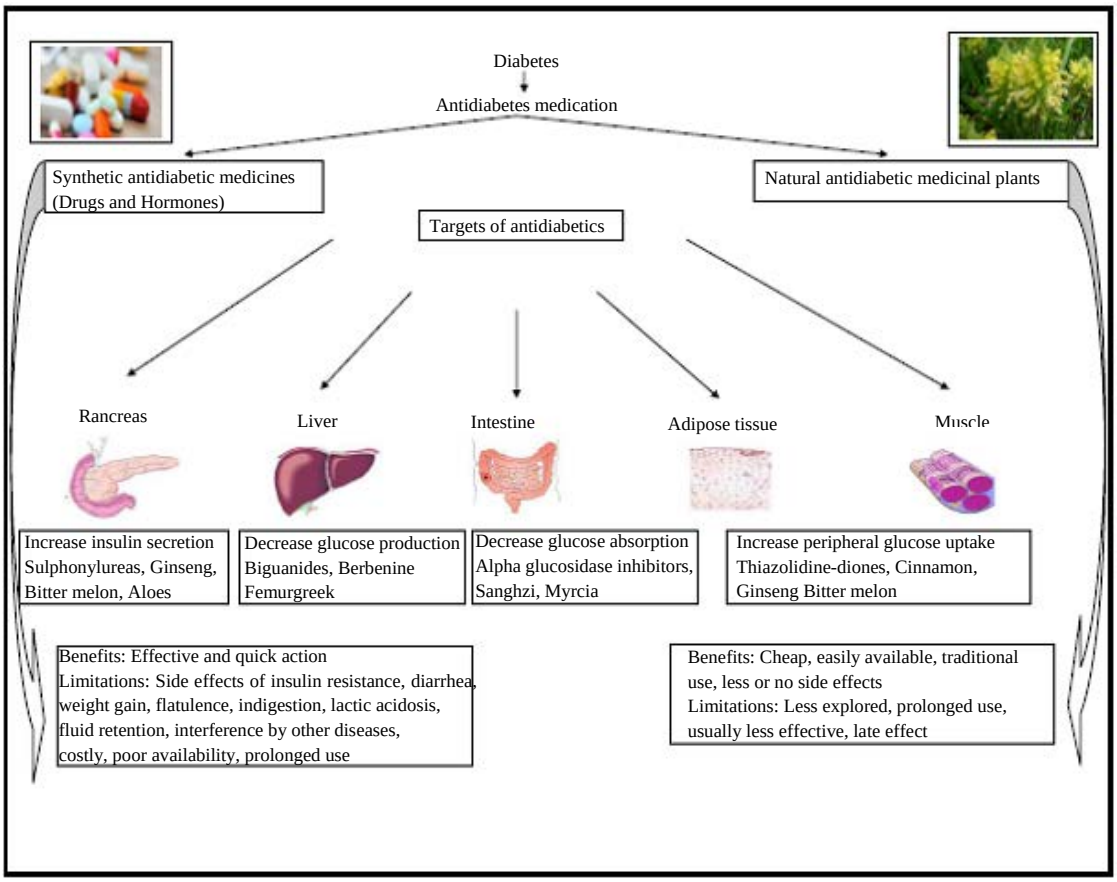

Fig. 1: Antidiabetic drugs and medicinal plants, their targets and mechanisms of action

reabsorption and brain insulin resistance/neurotransmitter dysfunction[170], therefore, current research on management of diabetes involves considering these alterations during drug development. GLP-1 receptor agonists, long-acting DPP-4 inhibitors, insulin secretagogues: TAK-875, SGLT-2 and SGLT-1 inhibitors, New Met (Metformin-delayed release), insulin sensitizers, mitochondrial target of TZDs, pyruvate dehydrogenase kinase inhibitors, protein tyrosine phosphatase 1B inhibitors, fibroblast growth factor-21, 11-β-hydroxysteroid dehydrogenase-1 inhibitors, diacylglycerolacyl transferase-1 inhibitors, anti-inflammatory therapies, glucagon receptor antagonists, glucokinase activators, fructose-1,6-bisphosphatase inhibitors, acetyl-CoA carboxylase inhibitors, other oral antidiabetic therapies (bile acid sequestrants, activators of the bile acid farnesoid X receptor, AMPK activators, modulators of the gut microbiota, activators of

glycogen synthase, inhibitors of glycogen phosphorylase and ranolazine), anti-obesity medications [(Qsymia (combination phentermine/topiramate XR) and Belviq (lorcaserin)] are under focus for research in present times[170].

Some have explored blood glucose-lowering medicinal herbs that have the ability to modulate one or more of the pathways that regulate insulin resistance, cell function, GLP-1 homeostasis and glucose (re)absorption[163]. However there are around 410 experimentally proven medicinal plants having antidiabetic properties but the complete mechanism of action is available only for about 109. There are several medicinal plants whose extract modulate glycolysis, Krebs cycle, gluconeogenesis, HMP shunt pathway, glycogen synthesis and their degradation, cholesterol synthesis, metabolism and absorption of carbohydrates and synthesis and release of insulin[171,165]. So there is enough scope for exploration and evaluation of novel therapeutic modalities with special emphasis on newest target specific interventions for better management of diabetes.

CONCLUSION

Diabetes has become a serious and rapidly spreading health problem all over the world with developing countries under major threat. Despite development of various types of drugs and continuous research on different fronts both number of cases and prevalence of diabetes are continuously increasing. Synthetic drugs, both chemical and hormones, are the main antidiabetic medicines currently used on large scale with majority being effective but cost, availability and concerns of side effects need to be addressed. Development of newer classes of antidiabetic drugs with novel targets, methods of administration and delivery has become the focus of current research. To cope concerns; research in alternative fields of therapy and drug development especially utilizing natural medicinal plants for diabetes management is gaining pace. These being cheaper, easily available, without side effects and utilized regularly, have great promise for diabetes cure. Advancement in medicinal plant research has enabled development of newer drugs and explored novel entities for specific targeting. However further research is needed in this field for proper evaluation at molecular, physiological, prophylactic and therapeutic levels for better management of this chronic and worldwide disease.

SIGNIFICANCE STATEMENT

Diabetes is a chronic disease with global prevalence and rising incidence. Herbal plants are being used for both prophylactic and therapeutic management of diabetes. The proper remedy of diabetes or its complications requires elaborative exploration and pharmacological evaluation for any prophylactic or therapeutic protocols. It also requires the presence of constituents with pharmacological safety for the betterment of diabetic patients or the predisposed ones. Advancement in herbal medicinal plant research has enabled development of newer drugs and explore novel entities for specific targeting.

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