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Medicinal Herbal Plants and Allopathic Drugs to Treat Diabetes Mellitus: A glance

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Review Article

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Abstract

The present study was based on Diabetes Mellitus, its cure using herbal drugs over allopathic drugs. According to the official World Health Organisation (WHO) data, India tops the list of countries with the highest number of diabetics; China, America, Indonesia, Japan, Pakistan, Russia, Brazil, Italy and Bangladesh follow. In the year 2000, the total number of diabetics in India stood at 31.7 million and is expected to rise by more than 100% in the year 2030 to account to a whopping 79.4 million. Despite the use of advanced Allopathic drugs for the treatment, use of herbal remedies is gaining higher importance because of Allopathic drugs have drawbacks and limitations. Natural herbs have been highly esteemed source of medicine throughout the human history. They are widely used today indicating that herbs are a growing part of modern high-tech medicine. The herbal drugs with anti-diabetic activity are extensively formulated commercially because of easy availability, affordability and less side effects as compared to the synthetic anti-diabetic drugs. The WHO has listed 21,000 plants, which are used for medicinal purposes around the world. A list of medicinal herbal plants with proven anti-diabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. Thus, this review article undertakes the attempt for providing updated information on the type of diabetes and herbal formulations which will enhance the existing knowledge of the researchers.

Keywords: India; *Ocimum Sanctum*; Anti-Oxidant; Clinical Trial; Newer Anti-Diabetic Drugs

Abbreviations: GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; GLUT4: Glucose Transporter-4; GSH: Glutathione; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; IL: Interleukin; INOS: Inducible Nitric Oxide Synthase; IRS: Insulin Receptor Substrate; LXRα: Liver X Receptor α; MAPK: Mitogen-Activated Protein Kinases; NF-κB: Nuclear Factor-κB; PPAR: Peroxisome Proliferator-Activated Receptor; PTP1B: Protein Tyrosine Phosphatase 1B; SGLT2: Sodium-Glucose Cotransporter-2; TGF: Transforming Growth Factor; AMPK: AMP-Activated Protein Kinase; CAP: C-Cbl-Associated Protein; DDP-4: Dipeptidyl Peptidase-4; AGEs: Advanced Glycation End Products.

Introduction

Many traditional medicines in use are derived from medicinal plants, minerals and organic matter [1]. A number of medicinal plants, traditionally used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems [2]. In Indian systems of medicine most practitioners formulate and dispense their own recipes [3]. The WHO has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world [3]. The current review focuses on herbal drug preparations and plants used in the treatment of diabetes mellitus, a major crippling disease in the world leading to huge economic losses.

Diabetes

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries. Studies conducted in India in the last decade have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population [4]. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 60 million by the year 2025. Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type-1 diabetes is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin while patients suffering from type-2 diabetes are unable to respond to insulin and can be treated with dietary changes, exercise and medication (Figure 1) [5]. Type-2 diabetes is the more common form of diabetes constituting 92% of the diabetic population. During diabetes, lipoproteins are oxidized by free radicals. There are also multiple abnormalities of lipoprotein metabolism in very low-density lipoprotein, low density lipoprotein, and high-density lipoprotein in diabetes [6]. Lipid peroxidation is enhanced due to increased oxidative stress in diabetic condition. Apart from this, advanced glycation end products (AGEs) are formed by non-enzymatic glycosylation of proteins. AGEs tend to accumulate on long-lived molecules in tissues and generate abnormalities in cell and tissue functions. In addition, AGEs also contribute to increased vascular permeability in both micro-vascular and macro-vascular structures by binding to specific macrophage receptors. This results in formation of free radicals and endothelial dysfunction. AGEs are also formed on nucleic acids and histones and may cause mutations and altered gene expression [7]. As diabetes is a multifactorial disease leading to several complications, and therefore demands a multiple therapeutic approach. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total lack of insulin, patients are given insulin injections. Whereas in case of those where cells do not respond to insulin many different drugs are developed taking into consideration possible disturbances in carbohydrate-metabolism. For example, to manage post-prandial hyperglycaemia at digestive level, glucosidase inhibitors such as acarbose, miglitol and voglibose are used. These inhibit degradation of carbohydrates thereby reducing the glucose absorption by the cells. To enhance glucose uptake by peripheral cells biguanide such as metphormine is used. Sulphonylureas like glibenclamide is insulinotropic and works as secretogogue for pancreatic cells. Although several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycaemia, weight gain, gastrointestinal disturbances, liver toxicity etc (Table 1) [8]. Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable anti-diabetic and antioxidant therapy. The hypoglycaemic effect of some herbal extracts has been confirmed in human and animal models of type-2 diabetes mellitus (Table 2). The WHO Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated.

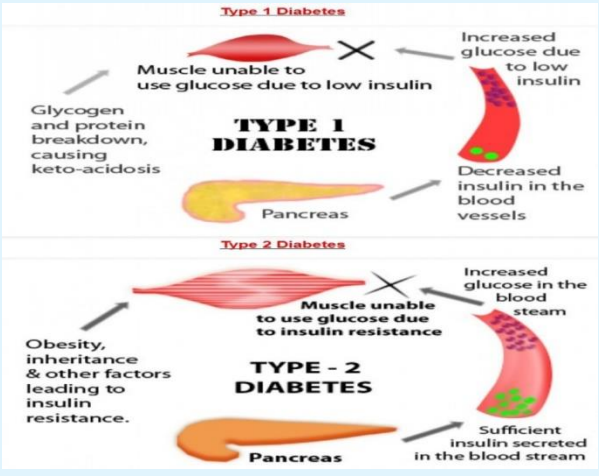

Figure 1: Type-1 and type-2 diabetes mellitus.

Class	Generic name and brand name	Mechanism of action	Adverse effects
Sulfonylureas	*Gliclazide* (Diamicron MR) *Glimepiride* (Amaryl) Glyburide (Diaβeta)	Stimulate the pancreas to produce more insulin	Hypoglycaemia (low blood sugar)
Meglitinides	*Metformine* (Glucophage) Metformine extended-release (Glumetza)	Reduce the production of glucose by the liver	Diarrhoea, metallic aftertaste, nausea
Thiazolidinediones (TZD)	*Pioglitazone* (Actos) Rosiglitazone (Avandia)	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver	Swelling due to water retention, weight gain Pioglitazone: increased risk of bladder cancer Rosiglitazone: increased risk of non-fatal heart attack
Alpha-glucosidases inhibitor	*Acarbose* (Glucobay)	low the absorption of carbohydrates (sugar) ingested	Bloating and flatulence (gaz)
Dipeptidyl-peptidase-4 (DPP-4) inhibitors	*Linagliptine* (Trajenta) Saxagliptine (OnglyzaMC) Sitagliptine (Januvia) Alogliptine (Nesina)	Intensify the effect of intestinal hormones (incretines) involved in the control of blood sugar	Pharyngitis, headache
Glucagon-like peptide-1 (GLP-1) agonist	*Exenatide extended-release* (Bydureon) Liraglutide (Victoza) Dulaglutide (Trulicity)	Mimic the effect of certain intestinal hormones (incretines) involved in the control of blood sugar	Nausea, diarrhoea, vomiting
Sodium glucose co-transporter -2 (SGLT-2) inhibitors	*Canaglifozine* (Invokana**)** Dapagliflozine (Forxiga) Empagliflozine (Jardiance)	Help eliminate glucose in the urine	Genital and urinary infections, more frequent urination

Table 1: Allopathic preparations, mechanism of actions and their adverse effects.

Scientific name	Common name	Family	Mechanism of action
Allium sativum	Garlic	Liliaceae	Improve plasma lipid metabolism and plasma antioxidant activity
Trigonella foenum graecum	Fenugreek	Fabaceae	Stimulate the secretion of insulin, reduce insulin resistance and decrease blood sugar levels
Aloe barbadensis	Aloe vera	Asphodelaceae	Improvement in impaired glucose tolerance
Tinospora cordifolia	Guduchi, gulvel	Menispermaceae	Decrease of glycaemia and brain lipids
Allium cepa	Onion	Liliaceae	Stimulating the effects on glucose utilization and antioxidant enzyme
Cinnamomum cassia	Cinnamon	Lauraceae	Increases the sensitivity of insulin receptor
Zingiber officinalis	Sunth	Zingiberaceae	Increases the insulin level
Carica papaya	Papaya	Caricaceae	Lowered fasting blood sugar, triglyceride, total cholesterol
Gymnema sylvestre	Gymnema, gudmar	Apocynaceae	Increase the serum G-peptide level which monitor the release of endogenous insulin
Azadirachta indica	Neem	Meliaceae	Glycogenolytic effect due to epinephrine action was blocked
Eugenia jambolana	Jamun	Myrataceae	Inhibited insulinase activity from liver and kidney
Mangifera indica	Mango	Anacardiaceae	Reduction in the intestinal absorption of glucose
Momordica charantia	Bitter gourd, melon	Cucurbitaceae	Activate PPARs alpha, y and lower the plasma apo

			beta-100 in mice fed with high fat diet
Ocimum sanctum	Holy basil, tulsi	Lamiaceae	Increased insulin release
Brassica juncea	Mustard	Brassicaceae	Increased activity of glycogen synthetase

Table 2: WHO has listed 15 medicinal herbal plants used in treatment of diabetes mellitus.

Allium Sativum (Garlic)

Garlic has been used in India for its anti-diabetic properties since ancient times [1]. In recent years, different in vitro and in vivo studies demonstrated garlic's anti-hyperglycaemic effects [9]. Reviewed the effects of garlic on several cardiovascular-related factors and its adverse effects; after analysing 45 randomized trials; they observed no effects on glycaemic-related outcomes. In their conclusions, the authors recommend future studies with clear definitions of constituents and preparations, because in these clinical trials there are great variations of samples (oil macerate, aged garlic, and different kinds of extracts) and doses (from 10mg to 10 g) with mice, observed that garlic extract antagonized LXRα, an important regulator of cholesterol, triglycerides, and glucose homeostasis, and increased LXRα expression in the intestine. These effects could have an important role in the reduction of the lipid profile by garlic, which would justify the potential for this treatment of diabetes, but it should be demonstrated in humans [10].

Trigonella Foenum Graecum (Fenugreek)

It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans [11]. Oral administration of 2 and 8 g/kg of plant extract produced dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats [12]. Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose −1, 6-biphosphatase activity [13]. This plant also shows antioxidant activity [14,15].

Aloe Barbadensis (Aloe Vera)

Anti-diabetic properties of Aloe vera selected a study with 72 diabetic women without drug therapy, divided into two groups. They received aloe vera gel (15 g) or placebo for 42 days. Blood glucose levels subsequently decreased from 250 mg to 141 mg/dL in the experimental group. The same research team investigated the effects of aloe vera gel in combination with a standard oral anti-diabetic therapy (2 × 5mg oral glibenclamide) and the subjects received either aloe or placebo as above. Results showed similar decreases in blood glucose in the actively treated group as described in the first trial. However, these studies were neither randomized nor blinded to patient or investigator [16].

Tinospora Cordifolia (Guduchi)

It is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of *Tinospora cordifolia* roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight [17]. *T. cordifolia* is widely used in Indian ayurvedic medicine for treating diabetes mellitus [18-20]. Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant anti-hyperglycaemic effect in different animal models, its effect was equivalent to only one unit/kg of insulin [21]. It is reported that the daily administration of either alcoholic or aqueous extract of *T. cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents [22].

Allium Cepa (Onion)

Dried onion powder shows anti-hyperglycaemic activity in diabetic rabbits. *Allium cepa* is also known to have antioxidant and hypolipidemic activity. Administration of a sulphur containing amino acid from *Allium cepa*, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase [23,24]. When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels [25].

Thea Sinesis (Tea)

Various studies report that polyphenolic compounds present in green and black tea are associated with

beneficial effects in the prevention of cardiovascular disease and anti-diabetic properties [26]. In this direction, different studies have been designed in order to identify the effects of tea on glucose metabolism and insulin signalling as well as possible positive effects on patients with established diabetes. The Women's Health Study described that tea drinkers (drinking ≥ 4 cups of tea/day) had a 30% lower risk for developing Type II DM vs. non-tea consuming women [27]. In the Japanese, who consume ≥ 4 cups of green tea daily, there is a 33% reduced risk for diabetes, but no reduction was observed for red or black tea reported the positive effect of black tea intake on different biomarkers in the serum of patients with Type II DM (total antioxidant capacity, MDA, C-reactive protein, and GSH levels) [28,29]. The positive effect of green tea was correlated with the continuous ingestion of catechin-rich beverages. In effect, in a double-blind, controlled study, patients with Type II DM without insulin therapy received green tea (582.8mg catechins or 96.3mg of catechins /day for 12 weeks) and at the end of the trial, there was an increase in insulin and a decrease in HbA1c levels in the catechin group vs. the control [30].

Sage Officinalis (Sage)

Leaves of *Sage officinalis* are used to treat digestive and metabolic disorders including Type II DM [31]. Their anti-hyperglycaemic effect has been studied in different animal model of diabetes and in a crossover trial with six healthy female volunteers as well as a 2-month randomized, double-blind [32,33], placebo-controlled trial, but no glycaemia was assayed [34]. However, two years later, the last authors evaluated the efficacy and safety of a sage leaf extract in the treatment of 86 hyperlipidaemic Type II DM patients using a randomized, placebo-controlled, parallel group study with 42 treated patients treated with leaf hydroethanolic extract (500 mg/8 h for 3 months) and 44 as placebo groups. In this case, fasting glucose and HbA1c values were determined, together with the lipidemic profile. They described that the leaf extract lowered fasting glucose and HbA1c compared to the baseline at the endpoint with no adverse effects reported. Therefore, they concluded that sage leaves might be safe and have anti-hyperglycaemic effects in hyperlipidaemic Type II DM patients since the lipidemic profile also improved [35].

Psidium Guajava (Guava)

Guava is a food crop and herbal plant from tropical countries whose leaves (water extract) are used to reduce hyperglycaemia in diabetic patients in Mexico. Many papers describing its pharmacological activities have been published, and Gutiérrez, et al. [36] reported two clinical assays. In one paper in China, a multicentric, randomized, controlled trial evaluated the efficacy of guava in diabetes management. After oral administration of 500 mg of aqueous leaf extract to 50 diabetic patients, they considered that guava could be used as a complementary therapy for preventing and treating diabetes mellitus, but not as a principal agent, since it is less effective than standard drugs. In the second trial, oral administration of 500 mg (fruit) to 40 patients decreased glycaemia after 3 weeks of treatment compared to the diabetic control group.

Gymnema Sylvestre (Gymnema)

The leaf of *Gymnema sylvestre* is a reputed herb in both Ayurvedic and Western medicines. It shows positive effects on blood sugar homeostasis and controls sugar cravings [37]. It acts through the stimulation of insulin secretion from pancreatic β cells, and some active compounds have been cited such as gymnemic acids and gurmarin, a 35-amino-acid peptide demonstrated that Gymnema showed a limited effect on GLP-1 levels, although other effects, such as the interaction with glyceraldehyde-3-phosphate dehydrogenase, a key enzyme in glycolysis pathway, have been described [38]. Complementary mechanisms were described for this species, such as the modulation of the enzymes responsible for glucose utilization (increased phosphorylase activity and decreased activity of gluconeogenic enzymes and sorbitol dehydrogenase) and inhibition of glucose absorption in the bowel [39]. Other effects of Gymnema extract include a prolonged hypoglycaemic action of exogenous insulin in dogs without a pancreas, intensification of effects of insulin, and extended duration of reduced glucose levels. These effects were observed after administration of the extract, the saponin fraction, or isolated triterpene glycosides [40]. Some of these properties have been confirmed in different clinical trials conducted in the US with a patented preparation based on a standardized extract (400 mg/day), but 27 patients with Type I DM with insulin therapy were studied, and it was concluded that Gymnema increases the endogenous levels of insulin, possibly due to pancreatic regeneration [39]. However, two small, open-label trials have also yielded promising results after administration of Gymnema to patients with Type II DM In the first trial, patients that received 200mg daily for 18 to 20 months of an ethanolic extract significantly improved fasting blood glucose and HbA1c levels. The second trial was uncontrolled, and patients that received 800 mg daily of a similar extract for 3 months reduced fasting blood glucose and HbA1c levels; however, they used a mixed population of 65 patients

with Type I and Type II DM. Gymnema reduced HbA1c levels and appears to improve glycaemic control, although complementary studies are necessary. In a later study, Type II DM patients received 500 mg herb/day for 3 months and the treated group reduced both fasting and postprandial blood glucose and HbA1c [40]. All together, these findings suggest that Gymnema extract could be beneficial for the management of diabetes mellitus.

Coffea Arabica (Coffee)

A seed of coffee, *Coffea arabica* intake is associated with a reduced risk of Type II DM. To confirm this property examined the long-term relationship between the consumption of coffee and other caffeinated beverages and the incidence of Type II DM in a prospective cohort study (The Nurses 'Health Study and Health Professionals' Follow-up Study). They followed up 41934 men (1986 to 1998) and 84276 women (1980 to 1998) without diabetes, and 1333 new cases of Type II DM in men and 4085 new cases in women were documented. They found an inverse association between coffee intake and Type II DM, thus suggesting that long-term coffee consumption is associated with a significantly lower risk for the disease [41]. This effect was associated with mineral and antioxidant contents, but the role of caffeine was not specified until the Pereira et al. study [42]. These authors demonstrated in a prospective analysis with a cohort of 28812 postmenopausal women free of diabetes of the Iowa Women's Health Study (1986–1997) that coffee intake, especially decaffeinated, was inversely associated with a risk of Type II DM.

Azadirachta Indica (Neem)

Hydroalcoholic extracts of this plant showed anti-hyperglycaemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemi diaphragm [43,44]. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and anti-oxidant effects [45].

Eugenia Jambolana (Jamun)

In India decoction of kernels of *Eugenia jambolana* is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Anti-hyperglycaemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood glucose level. This varies with different level of diabetes. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) it is reduced to 55.62% and 17.72% respectively. The extract of jamun pulp showed the hypoglycaemic activity in streptozotocin induced diabetic mice within 30 min of administration while the seed of the same fruit required 24 h. The oral administration of the extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney [46].

Mangifera indica (Mango)

The leaves of this plant are used as an anti-diabetic agent in Nigerian folk medicine, although when aqueous extract given orally did not alter blood glucose level in either normoglycaemic or streptozotocin induced diabetic rats. However, anti-diabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results indicate that aqueous extract of *Mangifera indica* possess hypoglycaemic activity. This may be due to an intestinal reduction of the absorption of glucose [47].

Momordica Charantia (Bitter Gourd)

Momordica charantia is commonly used as an anti-diabetic and anti-hyperglycaemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycaemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycaemic effect when administered subcutaneously to langurs and humans [48]. Ethanolic extracts of *M. charantia* (200 mg/kg) showed an anti-hyperglycaemic and also hypoglycaemic effect in normal and streptozotocin induced diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6-biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities [49].

Ocimum Sanctum (Holy Basil)

It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves of *Ocimum sanctum* showed the significant reduction in blood sugar level in both normal and alloxan induced diabetic rats [50]. Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicated the hypoglycaemic and hypolipidemic effects of tulsi in diabetic rats [51]. Oral administration of plant

extract (200 mg/kg) for 30 days led to decrease in the plasma glucose level by approximately 9.06 and 26.4% on 15 and 30 days of the experiment respectively. Renal glycogen content increased 10-fold while skeletal muscle and hepatic glycogen levels decreased by 68 and 75% respectively in diabetic rats as compared to control [52]. This plant also showed anti-asthmatic, anti-stress, anti-bacterial, anti-fungal, anti-viral, anti-tumor, gastric anti-ulcer activity, anti-oxidant, anti-mutagenic and immunostimulant activities.

Anti-Diabetic Drugs

Newer Anti-Diabetic Agents

- **Insulin secretagogues:** Newer sulphonylureas – glimepiride, Non-sulphonylureas – repaglinide, GLP-1 Receptor agonist- exenatide and liraglutide
- **Insulin sensitizers:** Biguanides (PPAR(α) antagonist) – fibrates, Rexinoids (PPAR(γ) antagonists) – thiazolidinediones, Protein tyrosine kinase inhibitors, Anti-obesity drugs, B-3 receptor antagonists
- **Inhibitors of intermediary metabolism:** Anti-lipolytic and anti-hyperlipidaemic drugs, Fatty acid oxidation inhibitors- Lisophyllin
- **Inhibitors of GI glucose absorption:** Glucosidase inhibitors, Amylin analogues-Pramlintide
- **Insulinomimetic drugs:** Vanadium salts

Glimeperide

This is a third generation SU which binds to a 65 kd protein of the putative SU receptor different from the 140 kd protein targeted by other SU [53]. It has a 3-fold faster rate of association and nine-fold faster rate of dissociation than glibenclamide and thus has rapid onset and prolonged duration of action, permitting once daily administration. Though its initial action is stimulation of insulin secretion, it has also an insulin-mimetic effect in peripheral tissues possibly mediated by GLUT-4 recruitment [54]. The extrapancreatic effects may explain lesser degree of stimulated hyperinsulinaemia. Unlike glibenclamide, this drug prevents post-exercise insulin release, thereby decreasing the risk of hypoglycaemia. It is absorbed completely in either fasting or fed state. It does not accumulate in the body with reducing renal function (up to GFR 10 ml/min) and its hydroxy metabolite has negligible effects on blood glucose and is excreted equally by the liver and kidney. Hence it is safe in renal failure and in the elderly. It does not exhibit any drug interaction and because of its poor binding to extra pancreatic, myocardial, and vascular system ATP dependent K+ channels, the risk of coronary vasoconstriction and adverse cardiovascular events are reduced in comparison to other SU's. On a weight for weight basis glimeperide is the most potent SU with suggested doses between 1-6 mg once daily, but doses up to 8 mg may give additional glucose lowering effect [55].

Repaglinide

Repaglinide is a new chemical entity, a carbamoymethyl benzoic acid derivative which differs structurally from the sulphonylureas and belongs to the meglinitide group of drugs [56]. The insulinotropic action of repaglinide is mediated via the inhibition of ATP dependent potassium ion channels in the pancreatic beta cell membrane which results in the depolarisation of the cell membrane and an influx of calcium ions through voltage-gated calcium channels. Intracellular calcium concentration is therefore increased and along with it, the insulin secretion. Repaglinide binds with high affinity to a receptor which is distinct from sulphonylurea receptor. In addition, repaglinide binds with low affinity to the classic sulphonylurea receptor. This differential binding results in more potent stimulation of insulin release. It is rapidly absorbed from the GI tract and has a half-life of less than 1 hour. It is metabolised primarily in the liver and is excreted predominantly in the bile thus, it is safer in renal failure and the elderly [57]. It is an effective post prandial glucose regulator and can be administered 3 times a day before meals for an effective glycaemic control. Doses may vary from 1-4 mg twice or thrice a day. Adverse effects include GI intolerance and hypoglycaemia, though the latter is not prolonged as with glibenclamide [58].

Glucagon Like Peptide (GLP-1)

The currently GLP-1 receptor agonists available are exenatide and liraglutide. These drugs exhibit increased resistance to enzymatic degradation by DPP4. In young patients with recent diagnosis of Type II DM, central obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 analogues that would have a beneficial effect on weight loss and improve the metabolic dysfunction. GLP-1 analogues are contraindicated in renal failure.

Exenatide

Exenatide, an exendin-4 mimetic with 53% sequence homology to native GLP-1, is currently approved for T2DM treatment as a single drug in the US and in combination with metformin ± sulfonylurea. Because of its half-life of 2.4 hour, exenatide is advised for twice-daily dosing. Treatment with 10μg exenatide, as an add-on to metformin, resulted in significant weight loss (−2.8 kg) in comparison to patients previously treated with

metformin alone. Exenatide is generally well tolerated, with mild to moderate gastrointestinal effects being the most common adverse effect.

Liraglutide

Liraglutide is a GLP-1 analogue that shares 97% sequence identity to native GLP-1. Liraglutide has a long duration of action (24 h). Liraglutide causes 1.5% decrease in HbA1C in individuals with Type II DM, when used as monotherapy or in combination with one or more selected oral anti-diabetic drugs. Liraglutide decreases body weight; the greatest weight loss resulted from treatment with liraglutide in combination with combined metformin/sulfonylurea (−3.24 kg with 1.8 mg liraglutide). Liraglutide also diminishes systolic pressure (mean decrease −2.1 to −6.7 mmHg). Liraglutide is well tolerated, with only nausea and minor hypoglycaemia (risk increased with use of sulfonylureas). Serum antibody formation was very low in patients treated with once-weekly GLP-1 receptor agonists. The formation of these antibodies did not decrease efficacy of their actions on blood glucose lowering [59].

Biguanides

They were introduced in 1958. Following UGDP study, they were out of favour because of fear of lactic acidosis, but have bounced back as they are known to significantly counteract insulin resistance. Metformin is preferred to phenformin as it does not inhibit mitochondrial oxidation of lactate and lactic acidosis with this drug is a rarity. Significant improvement in glycaemic control, lipid profile, and with no notable increase in plasma lactate, serum insulin, weight gain, and frequency of hypoglycaemia have been observed with this group of drugs [60].

Thiazolidinediones

The discovery of peroxisome proliferator activated receptor (PPAR) and their subtypes have led to the discovery of a new generation of drugs. The two major PPAR receptors are α & γ and both are expressed by obligate heterodimerisation with retinoic acid x receptor (Rx Rα and Rx Rγ). The PPAR (α) is primarily responsible for lipolysis by activation of enzymes such as acy lCOA oxidase, lipoprotein lipase, malic enzyme, bifunctional enzyme, and medium chain acy lCOA dehydrogenase. On the other hand, PPAR(γ) is primarily responsible for the adipocyte differentiation and at the metabolic level, in FFA and lipid anabolism and storage. The pronounced hypoglycaemic effect seen by PPAR(γ) agonists is attributed primarily to adiposite differentiation and/or activation [61].

Acarbose

Originally developed in Germany, is being widely used for post prandial glucose regulation. It is usually used in type 2 diabetes either as a monotherapy or in conjunction with SU's or biguanides. The average decrease in post-prandial blood glucose during acarbose treatment in diet treated type 2 diabetic patients was 3 mmol/ 1 and maximal decrease in HbA1C was 1%. Acarbose is recommended thrice daily in doses of 50-200 mg with the first bite of each major meal. Titration of dose is important to optimise benefits and minimise its side effects, which include flatulence, cramping, and diarrhoea [62].

Miglitol

This is a newer-glucosidase inhibitor, derived from 1-deoxy nojirimycin and is structurally similar to glucose. It is almost completely absorbed from GI tract, is short acting and hence is expected to have less GI side effects than acarbose. The usual dose is 50-100 mg. daily [63].

Vanadium salts

Vanadium is an ultra-trace element. Its compounds such as vanadyle orthovandate, metavandate and peroxovandate have been shown to have insulinomimetic effects on adipocytes, hepatocytes, and the skeletal muscles as well as in hypoinsulinaemic animal models of the diabetes. They act by a mechanism independent of insulin and near euglycaemia is achieved in animal models within 1-2 weeks. In animal models, vanadium salts induce decrease in body weight, attributed to its central anorectic effects. These salts act by increasing the phosphorylation of insulin receptor either by activation of the intrinsic tyrosine kinase activity or by inhibition of the phosphotyrosyl phosphatase that dephosphorylates the receptor and may also act on post receptor sites (mitogen activated protein kinase and cytosolic insulin independent tyrosine kinase). Importantly these compounds are effective even in situations where the insulin signal transduction pathway is defective. Usual dosage is 100 mg/day and the effect last for up to 2 weeks after discontinuation. Major side effects are gastrointestinal; however, there are fears of its mitogenic potential, as it stimulates tyrosine kinase. A synthetic organic complex of vanadyl (bis maltatato) oxovanadium with high lipophilicity and peroxovanadium compounds appear promising [64]. IGF-1 receptor agonists are also being developed for selective hypoglycaemic action, prolonged duration of effects, and perhaps for use by the oral route. Additionally, new drugs are being developed to counter complications in diabetes. These include

aminoguanidine, tenisetam, OPB-9195 which are AGE receptor antagonists; protein kinase C inhibitors (LYS 333531, WAY 151003, and Cremophor EL), nerve growth factors, octreotide, hismanal, topical clonidine, picotamide, and a lot of research is focused on antioxidants such as vitamin E and α- lipoic acid [65].

Pramlintide

Pramlintide is a synthetic amylin analogue that is indicated as an adjunct to mealtime insulin therapy in patients with Type I and Type II DM. By acting as an amylinomimetic, pramlintide delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety [66]. Pramlintide is administered by subcutaneous injection and should be injected immediately prior to meals. When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals to avoid a risk of severe hypoglycaemia. Pramlintide may not be mixed in the same syringe with any insulin preparation. Pramlintide should not be given to patients with diabetic gastroparesis (delayed stomach emptying) or a history of hypoglycaemic unawareness [67-85].

Conclusion

Diabetes mellitus is a most common endocrine disorder, affecting millions of people worldwide. Increase in the number of diabetic patients, high cost for medical treatments, unsatisfactory treatment response and mistrust of people in present day health care facilities signifies the still incomplete nature of the modern medicinal system. The aim of this article is to informed that western medicine and Indian traditional medicinal herbs available in market for the treatment of diabetes mellitus. For this, therapies developed along the principles of western medicine (Allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing countries like India. Medicinal herbal plants are used to manage type-1 and type-2 diabetes mellitus and their complications. Medicinal herbal plants therapy for diabetes has been followed all over the World successfully.

References

1. Grover JK, Yadav S, Vats V (2002) Medicinal plants of India with antidiabetic potential J Ethnopharmacol 81(1): 81-100.

2. Scartezzini P, Sproni E (2000) Review on some plants of Indian traditional medicine with antioxidant activity J Ethnopharmacol 71(1-2): 23-43.

3. Seth SD, Sharma B (2004) Medicinal plants of India. Indian J Med Res 120(1): 9-11.

4. Ramachandran A, Snehalatha C, Viswanathan V (2002) Burden of type 2 diabetes and its complications- the Indian scenario Curr Sci 83:1471-1476.

5. Matteucci E, Giampietro O (2000) Oxidative stress in families of type 1 diabetic patients. Diabetes Care 23(8): 1182-1186.

6. Brownlee M (1996) Advanced protein glycosylation in diabetes in diabetes and ageing. Ann Rev Med 46: 223-234.

7. Elgawish A, Glomb M, Friendlander M, Monnier VM (1999) Involvement of hydrogen peroxide in collagen cross-linking by high glucose in vitro and in vivo J Biol Chem 271: 12964-12971.

8. Dey L, Anoja SA, Yuan C-S (2002) Alternative therapies for type 2 diabetes. Alternative Med Rev 7(1): 45-58.

9. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, et al. (2001) Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med 161(6): 813-824.

10. Mohammadi A, Oshaghi EA (2014) Effect of garlic on lipid profile and expression of LXR alpha in intestine and liver of hypercholesterolemic mice. J Diabetes Metab Disord 13: 20.

11. Sauvaire Y, Petit P, Broca C, Manteghetti M, Baissac Y, et al. (1998) 4-hydroxyisoleucine: a novel amino acid potentiator of insulin secretion. Diabetes 47(2): 206-210.

12. Khosla P, Gupta DD, Nagpal RK (1995) Effect of Trigonellafoenumgraecum (fenugreek) on blood glucose in normal and diabetic rats. Indian J Physiol Pharmacol 39(2): 173-174.

13. Gupta D, Raju J, Baquer NZ (1999) Modulation of some gluconeogenic enzyme activities in diabetic rat liver and kidney: effect of antidiabetic compounds. Indian J Expt Biol 37: 196-199.

14. Ravikumar P, Anuradha CV (1999) Effect of fenugreek seeds on blood lipid peroxidation and antioxidants in diabetic rats. Phytother Res 13(3): 197-201.

15. Dixit PP, Ghaskadbi SS, Hari M, Devasagayam TPA (2005) Antioxidant properties of germinated fenugreek seeds. Phytother Res 19(11): 977-983.

16. Vogler BK, Ernst E (1999) Aloe vera: a systematic review of its clinical effectiveness. Br J Gen Pract 49(447): 823-828.

17. Stanely P, Prince M, Menon VP (2003) Hypoglycemic and hypolipidemic action of alcohol extract of Tinosporacordifolia roots in chemical induced diabetes in rats. Phytother Res 17(4): 410-413.

18. Stanely M, Prince P, Menon V (2001) Antioxidant action of Tinosporacordifolia root extract in alloxan diabetic rats. Phytother Res 15(3): 213-218.

19. Price PS, Menon VP (1999) Antioxidant activity of Tinosporacordifolia roots in experimental diabetes. J Ethnopharmacol 65(3): 277-281.

20. Mathew S, Kuttan G (1997) Antioxidant activity of Tinosporacordifolia and its usefulness in the amelioration of cyclophosphamide-induced toxicity. J Exp Clin Cancer Res 16(4): 407-411.

21. Dhaliwal KS (1999) "Inventor. Method and composition for treatment of diabetes," US Patent. 5886029.

22. Gupta SS, Varma SCL, Garg VP, Rai M (1967) Antidiabetic effect of Tinosporacordifolia. I. Effect on fasting blood sugar level, glucose tolerence and adrenaline induced hyperglycemia. Indian J Exp Biol 55: 733-745.

23. Roman-Ramos R, Flores-Saenz JL, Alaricon-Aguilar FJ (1995) Antihyperglycemic effect of some edible plants. J Ethnopharmacol 48(1): 25-32.

24. Kumari K, Mathew BC, Augusti KT (1995) Antidiabetic and hypolipidaemic effects of S-methyl cysteine sulfoxide, isolated from Allium cepa Linn. Ind. J. Biochem. Biophys 32(1): 49-54.

25. Mathew PT, Augusti KT (1975) Hypoglycemic effects of onion, Allium cepa Linn. on diabetes mellitus- a preliminary report. Ind J Physiol Pharmacol 19(4): 213-217.

26. Khan N, Mukhtar H (2013) Tea and health: studies in humans. Curr Pharm Des 19(34): 6141-6147.

27. Song Y, Manson JE, Buring JE, Sesso HD, Liu S (2005) Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. J Am Coll Nutr 24(5): 376-384.

28. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A (2006) The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 144(8): 554-562.

29. Neyestani TR, Shariatzade N, Kalayi A, Gharavi A, Khalaji N, et al. (2010) Regular daily intake of black tea improves oxidative stress biomarkers and decreases serum C-reactive protein levels in type 2 diabetic patients. Ann Nutr Metabol 57(1): 40-49.

30. Nagao T, Meguro S, Hase T, Otsuka K, Komikado M, et al. (2009) A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. Obesity (Silver Spring) 17(2): 310-317.

31. Kianbakht S, Dabaghian FH (2013) Improved glycemic control and lipid profile in hyperlipidemic type 2 diabetic patients consuming Salvia officinalis L. leaf extract: a randomized placebo. Controlled clinical trial. Complement Ther Med 21(5): 441-446.

32. Eidi M, Eidi A, Zamanizadeh H (2005) Effect of Salvia officinalis L. leaves on serum glucose and insulin in healthy and streptozocin-induced diabetic rats. J Ethnopharmacol 100(3): 310-313.

33. Lima CF, AzevedoMF, Araujo R, Fernandes-Ferreira M, Pereira-Wilson C (2006) Metformine-like effect of Salvia officinalis (common sage): is it useful in diabetes prevention? Br J Nutr 96(2): 326-333.

34. Sa CM, Ramos AA, Azevedo MF, Lima CF, Fernandes-Ferreira M, et al. (2009) Sage tea drinking improves lipid profile and antioxidant defences in humans. Int J Mol Sci 10(9): 3937-3950.

35. Kianbakht S, Abasi B, Perham M, Hashem Dabaghian F (2011) Antihyperlipidemic effects of Salvia officinalis L. leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clinical trial. Phytother Res 25(12): 1849-1853.

36. Gutiérrez RM, Mitchell S, Solis RV (2008) Psidium guajava: a review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol 117(1): 1-27.

37. Tiwari P, Mishra BN, Sangwan NS (2014) Phytochemical and pharmacological properties of Gymnema sylvestre: an important medicinal plant. Biomed Res Int, pp: 1-18.

38. Di Fabio G, Romanucci V, Zarrelli M, Giordano M, Zarrelli A (2013) C-4 gemdimethylatedoleanes of Gymnema sylvestre and their pharmacological activities. Molecules 18(12): 14892-14919.

39. Alqahtani A, Hamid K, Kam A, Wong KH, Abdelhak Z, et al. (2013) The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. Curr Med Chem 20(7): 908-993.

40. Kumar SN, Mani UV, Mani I (2010) An open label study on the supplementation of Gymnema sylvestre in type 2 diabetics. J Diet Suppl 7(3): 273-282.

41. Salazar-Martínez E, Willett WC, Ascherio A, Manson JE, Leitzmann MF, et al. (2004) Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med 140: 1-8.

42. Pereira MA, Parker ED, Folsom AR (2006) Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28812 postmenopausal women. Arch Intern Med 166(12): 1311-1316.

43. Chattopadhyay RR, Chattopadhyay RN, Nandy AK, Poddar G, Maitra SK (1987) Preliminary report on antihyperglycemic effect of fraction of fresh leaves of Azadiracta indica (Bengneem). Bull Calcutta Sch Trop Med 35: 29-33.

44. Chattopadhyay RR, Chattopadhyay RN, Nandy AK, Poddar G, Maitra SK (1987) The effect of fresh leaves of Azadiractaindica on glucose uptake and glycogen content in the isolated rat hemidiaphragm. Bull Calcutta Sch Trop Med 35: 8-12.

45. Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U (2002) Biological activities and medicinal properties of neem (Azadiracta indica). Curr Sci 82: 1336-1345.

46. Acherekar S, Kaklij GS, Kelkar SM (1991) Hypoglycemic activity of Eugenia jambolana and ficusbengalensis: mechanism of action. In vivo 5(2): 143-147.

47. Aderibigbe AO, Emudianughe TS, Lawal BA (1999) Antihyperglycemic effect of Mangiferaindica in rat.Phytother Res 13: 504-507.

48. Khanna P, Jain SC, Panagariya A, Dixit VP (1981) Hypoglycemic activity of polypeptide- p from a plant source. J Nat Prod 44(6): 648-655.

49. Shibib BA, Khan LA, Rahman R (1993) Hypoglycemic activity of Cocciniaindica and Momordicacharantia in diabetic rats: depression of the hepatic gluconeogenicenzymes glucose-6-phosphatase and fructose-1, 6-biphosphatase and elevation of liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. Biochem J 292(1): 267-270.

50. Vats V, Grover JK, Rathi SS (2002) Evaluation of antihyperglycemic and hypoglycemic effect ofTrigonellafoenum-graecum Linn, Ocimum sanctum Linn and Pterocarpusmarsupium Linn in normal and alloxanized diabetic rats. J Ethnopharmacol 79(1): 95-100.

51. Rai V, Iyer U, Mani UV (1997) Effect of Tulasi (Ocimum sanctum) leaf powder supplementation on blood sugar levels, serum lipids and tissue lipid in diabetic rats. Plant Food for Human Nutrition 50(1): 9-16.

52. Vats V, Yadav SP, Grover JK (2004) Ethanolic extract of Ocimum sanctum leaves partially attenuates streptozotocin induced alteration in glycogen content and carbohydrate metabolism in rats. J Ethnopharmacol 90(1): 155-160.

53. Draeger E (1995) Clinical profile of glimeperide. Diabetes Res Clin Pract 28 (1):139-146.

54. Muller G, Wied S (1993) The sulfonylurea drug glimepiride stimulates glucose transport, glucose tranporter translocation and dephosphorylation in insulin resistant rat adiocytes in vitro. Diabetes 42(12): 1852-1867.

55. Smits P, Thien T (1995) Cardiovascular effects of sulfonylurea derivatives. Implications for the treatment of NIDDM. Diabetologia 38(1): 116-121.

56. Feinglos RE (1999) Repaglinide therapy in treatment of type 2 diabetes. Theurapeutic Trends 17: 57-66.

57. Wolffenbuttel BHR, Graal MB (1996) New treatments for patients with type 2 diabetes mellitus. Postgrad Med J 72(853): 657-662.

58. Wolffenbuttel BHR, Nijst L, Sels JP, Menheere PP, Müller PG, et al. (2003) Effects of a new oral hypoglycemic agent, repaglinide on metabolic control in sulfonylurea-treated patients with NIDDM. Eur J Clin Pharmacol 45(2): 113-116.

59. Harris KB, McCarty DJ (2015) Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab 6(1): 3-18.

60. Huges TE, Balkan B, Villhauer ED (1999) NVP-DPP728 is a novel oral active dipeptidyl peptidase IV (DPP-IV) inhibitor prevents glucagon-likepeptide 1 (GLP-1) inactivation in rats. 42(11): 1324-1331.

61. Defronzo RA, Goodman AM (1995) Multicentre metformin study group. Efficacy of metformin in patients with noninsulin dependent diabetes mellitus. N Engl J Med 333(9): 541-546.

62. Bocl E (1999) Designing drugs for the treatment of diabetes in the next millennium. In: Kapur A, Joshi JK, (Eds.), Communication Workshop (P) Ltd, pp: 221.

63. Chiarson JC, Josse RG, Hunt JA, Palmason C, Rodger NW, et al. (1994) The efficacy of acrabose in the treatment of patients with insulin dependent diabetes mellitus a multicentric controlled clinical trial. Ann Intern Med 121(12): 928-935.

64. Segal P, Ferg PV, Scherthaner G, Ratzmann KP, Rybka J, et al. (1997) The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. Diabetes Care 20(5): 687-692.

65. Malabar UH, Dryden S, McCarthy HD (1994) Effects of chronic vandate administration in the STZ-induced diabetes rat. Diabetes 43(1): 9-15.

66. Chandalia HB, Lamba PS (2000) Futuristic antidiabetic agents. The Indian Practioner 53(1): 37-44.

67. Finkel Richard, Clark Michelle A, Cubeddu Luigi X (2009) Lippincott's Illustrated Reviews: Pharmacology, 4th (Edn.), pp: 290-291.

68. Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H (2018) Medicinal plants: past history and future perspective Journal of Herbmed Pharmacology 7(1): 1-7.

69. Islam D, Huque A, Mohanta LC (2018) Hypoglycemic and hypolipidemic effects of Nelumbo nucifera flower in Long-Evans rats. Journal of Herbmed Pharmacology 7(3): 148-154.

70. Asadi-Samani M, Bagheri N, Rafieian-Kopaei M (2017) Inhibition of Th1 and Th17 cells by medicinal plants and their derivatives: a systematic review. Phytotherapy Research 31: 1128-1139.

71. Savitskaya A, Yulia A Kononova, Aleksandra Yu Trofimova, Alina Yu Babenko, Daria A Savitskaya, et al. (2019) Predictors of Effectiveness of Glucagon-Like Peptide-1 Receptor Agonist Therapy in Patients with Type 2 Diabetes and Obesity. Journal of Dibetes Research 8: 1-12.

72. Jide Tian, Hoa Dang, Nataliya Karashchuk (2019) A Clinically Applicable Positive Allosteric Modulator of GABA Receptors Promotes Human β-Cell Replication and Survival as well as GABA's Ability to Inhibit Inflammatory T Cells. Journal of Dibetes Research 9: 1-7.

73. Marianne Pouwer G, Suvi Heinonen E, Margareta Behrendt, Anne-Christine Andréasson, Arianne van Koppen (2019) The APOE3-Leiden Heterozygous Glucokinase Knockout Mouse as Novel Translational Disease Model for Type 2 Diabetes, Dyslipidemia, and Diabetic Atherosclerosis. Journal of Dibetes Research 5: 1-13.

74. Mohammad SM, Tatsuhito H, Rieko I, Emiri Miura-Yura, Yuichiro Yamada, et al. (2019) Glucagon-Like Peptide-1 Receptor Agonist Protects Dorsal Root Ganglion Neurons against Oxidative Insult. Journal of Dibetes Research 7: 1-7.

75. Zhoujun Liu, Yu Chen, Guofang Chen (2019) Impaired Glucose Metabolism in Young Offspring of Female Rats with Hypothyroidism. Journal of Dibetes Research 12: 1-10.

76. Hunan Province, Zhao Hu, Fan Gao (2019) A Case-Control Study on Risk Factors and Their Interactions with Prediabetes among the Elderly in Rural Communities of Yiyang City. Journal of Dibetes Research 9: 1-8.

77. Moritsugu Kimura, Masao Toyoda, Nobumichi Saito (2019) A Liquid-Based Cytology System, without the Use of Cytocentrifugation, for Detection of Podocytes in Urine Samples of Patients with Diabetic Nephropathy. Journal of Dibetes Research 5: 1-7.

78. Érika RangelB, Cláudia Rodrigues O (2019) Micro- and Macrovascular Complications in Diabetes Mellitus: Preclinical and Clinical Studies. Journal of Dibetes Research 10: 1-5.

79. Junlin Zhang, Rui Zhang, Yiting Wang (2019) The Level of Serum Albumin Is Associated with Renal Prognosis in Patients with Diabetic Nephropathy. Journal of Dibetes Research 11: 1-9.

80. Shuo Qiu, Yachao Jia, Yunchu Sun, Pei Han, Gen Wen, et al. (2019) Von Hippel-Lindau (VHL) Protein Antagonist VH298 Improves Wound Healing in Streptozotocin-Induced Hyperglycaemic Rats by Activating Hypoxia-Inducible Factor- (HIF-) 1 Signalling. Journal of Dibetes Research 4: 1-10.

81. Zhen Qiu, Yuhong He, Hao Ming, Shaoqing Lei, Yan Leng, et al. (2019) Lipopolysaccharide (LPS) Aggravates High Glucose- and Hypoxia/Reoxygenation-Induced Injury through Activating ROS-Dependent NLRP3 Inflammasome-Mediated Pyroptosis in H9C2 Cardiomyocytes. Journal of Dibetes Research 7: 1-12.

82. Bo Zhao, Quan Yuan, Jia-bao Hou, Zhong-yuan Xia, Li-ying Zhan, et al. (2019) Inhibition of HDAC3 Ameliorates Cerebral Ischemia Reperfusion Injury in Diabetic Mice In Vivo and In Vitro. Journal of Dibetes Research 9: 1-12.

83. Fan Zheng, Suixin Liu, Yuan Liu, Lihua Deng (2019) Effects of an Outpatient Diabetes Self-Management Education on Patients with Type 2 Diabetes in China: A Randomized Controlled Trial. Journal of Dibetes Research 3: 1-7.

84. Satoshi Ida, Ryutaro Kaneko, Kazuya Murata, (2019) Utility of Real-Time and Retrospective Continuous Glucose Monitoring in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. Journal of Dibetes Research 3: 1-10.

85. Ju-yi Li, Zhong-jing Wang, Ai-ping Deng, Yu-ming Li (2019) ENA-78 Is a Novel Predictor of Wound Healing in Patients with Diabetic Foot Ulcers. Journal of Dibetes Research 8: 1-9.