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Review Article

A REVIEW OF HERBAL DRUGS AND PROSPECTIVE STUDIES FOR MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT
Diabetes mellitus (DM) is a metabolic disorder, occur when the pancreas does not make sufficient amount of insulin. Hyperglycaemia leads to severe injure especially the nerves and blood vessels (retinopathy, neuropathy, and nephropathy). According to World Health Organization the diabetic people is expected to increase up to 300 million or more by the year 2025. We searched the scientific database using various original research articles, clinical trials, meta analysis, patent reports, validation study, observational study, review articles published in PubMed, Scopus, Science direct and Google by using the keyword. After an initial search, 528 articles were identified, out of which 50 articles had required criteria for the comparative study and meta-analysis of related topics. Herbal plants were extremely venerated source of medicine in Ayurveda and now they have become a growing part of modern, high-tech medicine. It also reveals the information about the most recent innovation in the treatment of Type-I and Type II Diabetes mellitus. These reviews have proven that the herbal drugs were used for the treatment of Type II Diabetes mellitus worldwide. It also reveals that new approaches of nanotechnology were good choice for the management of Diabetes mellitus now a days. Hopefully, these new kind of treatment may help in making the everyday lives of millions of diabetes patients more comfortable.

Keywords: Diabetes mellitus, Nanotechnology, Hyperglycaemia, Pancreas.

1. INTRODUCTION
Diabetes mellitus (DM) is a group of metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidemia, polyuria, polyphagia and polydipsia. It is a chronic disease associated with abnormally high levels of glucose in the blood or deficit of insulin [1]. The pathogenesis is due to inadequate production of insulin or inadequate sensitivity of cells to the action of insulin. Hyperglycaemia damages many body systems, especially the nerves and blood vessels which lead to a microvascular (retinopathy, neuropathy and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications [2].

The disease is rapidly increasing worldwide and affecting all parts of the world [3]. Type 2 diabetes or non-insulin-dependent diabetes mellitus, is the most common form of the disease, accounting for 90%-95% of cases in which the body does not produce enough insulin [4]. According to World Health Organization the diabetic people is likely to increase up to 300 million or more by the year 2025 [5].

2. METHODS
We searched various original research articles, clinical trials, meta analysis, patent reports, validation study, observational study, review articles published in PubMed, Scopus, Science direct and Google by using the keyword "A Review of Diabetes mellitus or Herbal drug for Diabetes Mellitus or meta analysis of Prospective studies". The initial search identified 528 articles, of which 50 articles were selected, which were scrutinized for relevance.

3. HERBAL PLANTS FOR DIABETES MELLITUS
Herbal medicine is getting huge popularity both in developing and developed countries of the world because of their natural origin and less side effects. A number of medicinal plants traditionally used for over 1000 years in

Indian Ayuveda systems. These kind of medicinal drugs approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost.

3.1. *Acacia arabica* (Leguminosae)

The seed of *Acacia arabica* showed hypoglycaemic effect in rats through release of insulin. However, powdered seeds of *Acacia arabica* at 2, 3 and 4 g/kg, exert a significant hypoglycaemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells [6].

3.2. *Aegle marmelos* (Rutaceae)

Aqueous leaf extract of *Aegle marmelos* showed antidiabetic activity in streptozotocin induced diabetic rats after 14 days treatment either by increasing utilization of glucose or by direct stimulation of glucose uptake through increased secretion of insulin [7].

3.3. *Agrimony eupatoria* (Rosaceae)

Aqueous extract of *Agrimony eupatoria* evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line in vitro. The effect of extract be found to be glucose-independent [8].

3.4. *Alangium salvifolium* (Alangiaceae)

Methanolic extract of *Alangium salvifolium* leaves possesses antidiabetic and antihyperlipidemic effects in dexamethasone induced insulin resistance in rats, which may be due to the antioxidant and insulinotropic effect of extract [9].

3.5. *Aloe vera* (Liliaceae)

Hypoglycemic effect of *Aloe vera* in the rats is mediated through stimulation of synthesis or release of insulin from the beta-cells of Langerhans [10]. Effect of pseudoprototinosaponin AIII and prototinosaponins AIII on glucose uptake and insulin release suggested their hypoglycaemic effects are due to actions on hepatic gluconeogenesis or glycogenolysis [11, 12].

3.6. *Asparagus racemosus* (Liliaceae)

The ethanol extract, hexane, chloroform and ethyl acetate fractions of *Asparagus racemosus* root were shown to have dose-dependent insulin secretion in isolated perfused rat pancreas, isolated rat islet cells and clonal beta-cells. These observations reveal that the chemical constituents of *Asparagus racemosus* root extracts have insulinotropic activity [13].

3.7. *Bauhinia variegata* (Caesalpiniaceae)

The ethanolic extract of leaves of *Bauhinia variegata* and its major metabolite (6S, 7E, 9R)-9-hydroxymegastigma-4,7-dien-3-one-9-beta-glycopyraroside (roseoside) have insulinotropic activity in insulin-secreting cell line INS-1 and it was found to be dose-dependent [14].

3.8. *Biophytum sensitivum* (Oxalidaceae)

The leaf extract of the *Biophytum sensitivum* stimulates pancreatic beta cells to release insulin in diabetic male rabbits and exerts hypoglycemic activity. The hypoglycaemic activity may be mediated through stimulating the synthesis or release of insulin from the beta cells of Langerhans [15].

3.9. *Boerhaavia diffusa* (Nyctaginaceae)

The chloroform extracts of leaves of *Boerhaavia diffusa* showed antidiabetic activity in alloxan induced diabetic rats which mainly act by reducing blood glucose level and increasing insulin sensitivity [10].

3.10. *Bougainvillea spectabilis* (Nyctaginaceae)

The hypoglycaemic potential of ethanolic leaf extract of *Bougainvillea spectabilis* in streptozotocin-induced diabetic rats was observed possibly due to increased glucose uptake by improved glycogenesis in the liver and also due to improved insulin sensitivity [16].

3.11. *Cinnamon zeylaniucm* (Lauraceae)

In vitro incubation of pancreatic islets with cinnamaldehyde isolated from *Cinnamon zeylaniucm* resulted in improved insulin release. The insulinotropic effect of cinnamaldehyde was due to enhance in the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues [17].

3.12. *Catharanthus roseus* (Apocyaceae)

The methanolic extract of leaves and twigs of *Catharanthus roseus* enhances the insulin release from beta cell of Pancreas. The extract was also initiate to be helpful in prevention of injure caused by oxygen free radicals [10].

3.13. *Citrullus colocynthis* (Cucurbitaceae)

The ethanolic extract of the dried seedless pulp of *Citrullus colocynthis* at 300 mg/kg, p.o had insulinotropic actions in alloxan-induced diabetic rats [18]. Its aqueous extract showed dose-dependent increase in insulin release from isolated islets [10].

3.14. *Coccinia indica* (Cucurbitaceae)

Oral administration of dried extract of *Coccinia indica* at 500 mg/kg, p.o. for 6 weeks significantly increased insulin secretion. The plant extract reveals its beneficial hypoglycemic effect in experimental animals and human diabetic subject possibly through an insulin secreting effect or through influence of enzymes involved in glucose metabolism [12].

3.15. *Cornus officinalis* (Cornaceae)

The alcoholic extract of *Cornus officinalis* show increase GLUT4 mRNA and its protein expression in NIDDM rats by promoting creation of pancreatic islets and by increasing postprandial release of insulin and therefore accelerating the glucose transport [15]. Methanol extract and its fractions had potent insulin mimic activity on phosphoenolpyruvate carboxykinase expression [19].

3.16. *Eugenia jambolana* (Myrtaceae)

Effect of *Eugenia jambolana* seeds extract in isolated pancreatic islet cells of normal and diabetic animals was investigated and found that it enhances insulin secretion from cells. Its extract also inhibited insulinase activity from liver and kidney [12, 20].

3.17. *Ficus bengalensis* (Moraceae)

The oral administration of the extract of *Ficus bengalensis* caused better serum insulin levels in normoglycaemic and diabetic rats [12]. Blood sugar lowering activity of a dimethoxy derivative of leucocyandin 3-O-beta-d-galactosyl cellobioside at a dosage of 250 mg/kg, p.o. isolated from the bark of *Ficus bengalensis* in normal and moderately diabetic rats was mainly due to insulinomimetic activity [22].

3.18. *Ginkgo biloba* (Ginkgoaceae)

Effect of *Ginkgo biloba* extract in humans and healthy rats shows that it considerably increases the insulin concentration [12, 23].

3.19. *Gymnema sylvestre* (Asclepiadaceae)

The alcoholic extract of *Gymnema sylvestre* stimulates insulin secretion from the rat islets of Langerhans. Pancreatic beta cells may be regenerated or repaired in type II diabetic rats [24].

3.20. *Helicteres isora* (Sterculiaceae)

The Antihyperglycemic activity of butanol extracts of root of *Helicteres isora* at 250 mg/kg, p.o. in glucose loaded rats acts through insulin-sensitizing activity [25].

3.21. *Momordica charantia* (Cucurbitaceae)

The fresh fruit juice of *Momordica charantia* can result in considerable reduction of blood glucose level and increased conc. of plasma insulin in diabetic rats. The phytochemical constituents momordicin, charantin and a few compounds such as galactose-binding lectin and insulin-like protein isolated from various parts of this plant have insulin mimetic activity [6, 26].

3.22. *Mucuna pruriens* (Leguminosae)

The powdered seeds extract of *Mucuna pruriens* shows blood glucose lowering activity at 0.5, 1 and 2 g/kg, p.o. in normal rabbits as well as 1 and 2 g/kg, p.o. in alloxan-diabetic rabbits. It probably acts through stimulation of the release of insulin or by a direct insulin-like action due to the presence of trace elements like manganese, zinc, etc. [12, 27].

3.23. *Panax ginseng* (Araliaceae)

The roots of *Panax ginseng* consist of Ginseng polypeptides which were injected subcutaneously at daily doses of 50 and 100 mg/kg for 7 successive days in mice resulted in decreased blood glucose, increased liver glycogen level and stimulated insulin secretion [28].

3.24. *Pterocarpus marsupium* (Fabaceae)

The regeneration of pancreatic beta cell by flavonoid fraction from *Pterocarpus marsupium* has been observed. Epicatechin, its active principle, has been found to be insulinogenic thus enhancing insulin release and conversion of proinsulin to insulin *in vitro* [21].

3.25. *Radix rehmanniae* (Scrophulariaceae)

The rhizome of *Radix rehmanniae* exhibit the pectin type polysaccharide, which have hypoglycemic activity in normal and streptozotocin induced diabetic mice, it is possibly due to its stimulant activity of secretion of insulin and reducing the glycogen content in the mice [29].

3.26. *Syzygium cumini* (Rutaceae)

The fruit pulp extract of *Syzygium cumini* exerts hypoglycaemic activity on oral administration to normoglycemic and STZ induced diabetic rats, it was mediated by insulin secretion and inhibited insulinase activity [12].

3.27. *Trigonella foenum-graecum* (Leguminosae)

In vitro and *in vivo* experiments showed that *Trigonella foenum-graecum* has caused glucose-induced insulin release

[6]. A specific amino acid, hydroxyisoleucine of the free amino acids in its seeds, may possess insulin-stimulating properties [26]. Anti-diabetic effect have been linked to delayed gastric emptying caused by the high fiber content, inhibition of carbohydrate digestive enzymes and stimulation of insulin secretion [30].

3.28. *Ziziphus oenoplia* (L) mill (Rhamnaceae)

The aqueous and ethanolic extracts of *ziziphus oenoplia* (L) mill stem bark has hypoglycaemic activity against alloxan induce diabetic rats at 200 mg/kg and 400 mg/kg b.w. dose, the possible effect observer probably due to stimulation of the release of insulin from beta cell of langerhans [31].

3.29. *Zizyphus spina-christi* (Rhamnaceae)

The butanol extract of *Zizyphus spina-christi* leaves and its major saponin glycoside, christinin-A, on the serum glucose and insulin levels showed that christinin-A potentiated glucose-induced insulin release in non-diabetic control rats [12, 32].

Table 1: List of plants having antidiabetic activity

Sr. No	Name of Plant	Family	Part of Plant Used	Mechanism
1	*Acacia Arabica*	Leguminosae	Powdered seeds	Initiating the release of insulin from pancreatic beta cells [6]
2	*Aegle marmelos*	Rutaceae	Aqueous leaf extract	Increasing utilization of glucose or by direct stimulation of glucose uptake through increased insulin secretion [7]
3	*Agrimony eupatoria*	Rosaceae	Aqueous extract	Stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell [8]
4	*Alangium salvifolium*	Alangiaceae	Methanolic extract of leaves	Due to the antioxidant and insulinotropic effect of extract [9]
5	*Aloe vera*	Liliaceae	Gel	Stimulation of synthesis or release of insulin from the beta-cells of Langerhans [10-12]
6	*Asparagus racemosus*	Liliaceae	Root	Insulinotropic activity [13]
7	*Bauhinia variegate*	Caesalpiniaceae	Leaves	Insulinotropic activity [14]
8	*Biophytum sensitivum*	Oxalidaceae	Leaf extract	Stimulates pancreatic beta cells to release insulin [15]
9	*Boerhaavia diffusa*	Nyctaginaceae	Leaves extract	Act by reducing blood glucose level and increasing insulin sensitivity [10]
10	*Bougainvillea spectabilis*	Nyctaginaceae	Leaves	Increased glucose uptake by enhanced glycogenesis in the liver and also due to increased insulin sensitivity [16]
11	*Cinnamon zeylaniucm*	Lauraceae	Bark	Increase in the glucose uptake through glucose transporter (GLUT4) translocation in peripheral tissues [17]
12	*Catharanthus roseus*	Apocyaceae	Leaves and twigs	Enhance secretion of insulin [10]
13	*Citrullus colocynthis*	Cucurbitaceae	Pulp extract	Increase in insulin release from isolated islets [10, 18]
14	*Coccinia indica*	Cucurbitaceae	Whole plant	An insulin secreting effect or through influence of enzymes involved in glucose metabolism [12]
15	*Cornus officinalis*	Cornaceae	Whole plant	Increasing postprandial secretion of insulin and therefore accelerating the glucose transport [15, 19]
16	*Eugenia jambolana*	Myrtaceae	Seeds	Insulin secretion from cells [12, 20]
17	*Ficus bengalensis*	Moraceae	Fruit	Increased insulin secretion is mainly due to inhibited insulinase activity from liver and kidney [12, 22]
18	*Ginkgo biloba*	Ginkgoaceae	Plant	Increased the insulin concentration [12, 23]

19	*Gymnema sylvestre*	Asclepiadaceae	Leaves	Stimulated insulin secretion from the rat islets of Langerhans and several pancreatic beta cell lines [24]
20	*Helicteres isora*	Sterculiaceae	Fruits, Root	Insulin-sensitizing activity [25]
21	*Momordica charantia*	Cucurbitaceae	Fruit juice	Stimulates pancreatic insulin secretion [6, 26]
22	*Mucuna pruriens*	Leguminosae	Powdered seeds	Stimulation of the release of insulin [12, 27]
23	*Panax ginseng*	Araliaceae	Root	Significantly evoked a insulin release in a glucose-independent manner [28]
24	*Pterocarpus marsupium*	Fabaceae	Bark	Acts by regenerating the beta cells and may produce actions similar to that of insulin [21]
25	*Radix rehmanniae*	Scrophulariaceae	Rhizome	Stimulating the secretion of insulin and reducing the glycogen content in the mice [29]
26	*Syzygium cumini*	Rutaceae	Pulp	Insulin secretion and inhibited insulinase activity [12]
27	*Trigonella foenum-graecum*	Leguminosae	Seeds	Inhibition of Alpha amylase and Alpha Glucosidase enzyme and stimulation of insulin secretion [6, 26, 30]
28	*Ziziphus oenoplia (L) Mill*	Rhamnaceae	Bark	Stimulation of the release of insulin [31]
29	*Zizyphus spina-christi*	Rhamnaceae	Leaves	Serum insulin and pancreatic cAMP levels showed significant increase [12, 32]

4. APPLICATIONS OF NANOTECHNOLOGY IN TREATMENT OF DIABETES MELLITUS

Nanotechnology is a new modern technique that uses different methods to determine minute amounts of insulin and blood sugar level. This is a key step toward developing the ability to calculate the health of the body's insulin-producing cells. This can be achieved by adopting one of under mentioned methods [33].

4.1. Micro Physiometer

The Microphysiometer built as of multi walled carbon nano tubes, which are similar to several flat sheets of carbon atoms stack and roll into very small tubes. The nano tubes are electrically conductive and the concentration of insulin in the chamber can be directly linked to the current at the electrode and the nanotubes work consistently at pH levels characteristic of living cells. Current detection methods measure insulin production at intervals by periodically collecting small samples and measuring their insulin levels. The new sensor detects insulin levels continuously by measuring the transfer of electrons produced when insulin molecules oxidize in the presence of glucose. When the cells produce more insulin molecules the current in the sensor increases and *vice versa*, allowing monitoring insulin concentrations in real time [34].

4.2. Implantable sensor

Polyethylene glycol beads coated with fluorescent molecules used to monitor diabetes blood sugar levels. The beads are injected under the skin and stay in the interstitial fluid. When glucose in the interstitial fluid drops to dangerous levels, glucose displaces the fluorescent molecules and creates a glow. This glow is seen on a tattoo placed on the arm. Sensor microchips are also being developed to continuously monitor key body parameters including pulse, temperature and blood glucose. A chip would be implanted under the skin and transmit a signal that could be monitored continuously [35].

4.3. Oral insulin

The blood-sugar levels of patients can be control by insulin administration directly into the bloodstream using injections. This unpleasant method is required since stomach acid destroys protein-based Insulin. The new system is based on inhaling the insulin (instead of injecting it) and on a controlled release of insulin into the bloodstream [36].

Production of pharmaceutically active oral insulin, in large quantities has become feasible. The oral route is considered to be the most convenient and comfortable means for administration of insulin for less invasive and painless in diabetes management, leading to a higher patient compliance [37, 38]. Nevertheless, the intestinal epithelium is a major barrier to the absorption of hydrophilic drugs, as they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the bloodstream [39]. Therefore, attention has been

given to improving the para cellular transport of hydrophilic drugs [40, 41]. A variety of intestinal permeation enhancers like chitosan have been used for the assistance of the absorption of hydrophilic macromolecules [42]. Therefore, a carrier system is needed to protect protein drugs from the acidic environment in the stomach and small intestine [43]. Additionally, chitosan nanoparticles enhanced the intestinal absorption of protein molecules to a greater extent than aqueous solutions of chitosan *in vivo* [44].

4.4. Nanosphere for oral insulin production

The most promising strategy to achieve oral insulin is the use of a microsphere system which is inherently a combination strategy. Microspheres act both as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation within its matrix and as permeation enhancers by effectively crossing the epithelial layer after oral administration.

Radwant M.A. and Aboul-Enein H.Y. from Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, used polyethylcyanoacrylate (PECA) nanospheres as biodegradable polymeric carriers for oral delivery of insulin. The administration to streptozotocin-induced diabetic rats showed a very good hypoglycemic effect. Should the effect be proven in human research, it might significantly improve patient compliance [45].

4.5. Artificial Pancreas

Artificial pancreas could be the stable solution for diabetic patients. The theory of its work is based on a sensor electrode repeatedly measures the level of blood glucose and this information feeds into a small computer that energizes an infusion pump, and the needed units of insulin enter the bloodstream from a small reservoir. Since this reservoir we called "Nano robot" which would have insulin departed in inner chambers, and glucose-level sensors on the surface. When blood glucose levels increase, the sensors on the surface would record it and insulin would be released [46].

Another way to restore body glucose is the use of a tiny silicon box that contains pancreatic beta cells taken from animals. The box is surrounded by a material with a very specific nanopore size (about 20 nanometers in diameter). These pores are big enough to allow for glucose and insulin to pass through them, but small enough for passage of much larger immune system molecules. These boxes can be implanted under the skin of diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need of powerful immunosuppressant that can leave the patient at a serious risk of infection [47].

Table 2: Different methods and functions of nanotechnology for DM

Sr. No.	Methods	Specification	Functions
1	Micro Physiometer	Multi walled carbon nanotubes	Detection of insulin and blood sugar
2	Implantable sensor	Polyethylene glycol beads coated with fluorescent molecules	Monitor Diabetes blood sugar levels
3	Oral Insulin	Nanoparticles coated with mucoadhesive chitosan	The insulin released from Nanoparticle through the para cellular pathway to the bloodstream
4	Microsphere for oral insulin	Polyethylcyanoacrylate (PECA) nanospheres	Biodegradable polymeric carriers for oral delivery of insulin
5	Artificial Pancreas	Insulin departed in inner chambers, and Glucose-level sensors on the surface " Nanorobot"	When blood glucose levels increase, the sensors on the surface would record it and insulin would be released Yet, this kind of nano-artificial pancreas is still only a theory.
		Tiny silicon box	Box that contains pancreatic beta cells taken from animals.
		Insert new genes into naturally occurring cells	Artificial beta cell that will produce insulin in response to the rise of blood glucose
6	The Nano pump	The pump is composed of nanoetched silicon membranes with mesopores	The pump injects Insulin to the patient's body in a constant rate.
7	Smart Cell	Smart Cell protein matrix	When glucose rises in the bloodstream, it will eat away Smart Cell's structure. As the Smart Cell protein matrix breaks down, insulin is released

4.6. The Nano pump

The nano pump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by De biotech is in Insulin delivery. The pump injects Insulin to the patient's body at a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time. The pump is composed of nanoetched silicon membranes with mesopores that would allow insulin proteins out, but would be too small to allow in cells that would attack the implanted beta cells. This would allow the pump to continuosly produce insulin [48].

4.7. Smart Cell

Todd Zion from Nanostructure Materials Research Laboratory has developed technology for diabetes treatment called Smart Cell. When glucose rises in the bloodstream, it will eat away smart cell's structure. As the smart cell protein matrix breaks down, insulin is released. The more glucose is present, the faster matrix will erode. Smart cell technology means that diabetics could stop endlessly checking and rechecking their glucose levels, injecting more insulin as needed, because the drug will handle the chore. An injection a day is all that diabetics will need. No blood testing, no multiple shots. Early round of experiments with lab rats has begun, and the preliminary results are promising [49].

5. DISCUSSION

Diabetes is a disorder of carbohydrate, fat and protein metabolism. It is due to insufficient production of insulin or due to its inhibitory action, which can be considered as a most important cause of the disease which make their impact on the development of nations [51]. Before there were drugs from drug companies, natural cures were used and they can still be used today. There are many herbs with strong anti-diabetic properties. Herbal treatments for diabetes have been used in patients with insulin dependent and non-insulin dependent diabetes, diabetic retinopathy, diabetic neuropathy etc. The families of plants with the most potent hypoglycaemic effects include Leguminoseae, Rutaceae, Rosaceae, Liliaceae, Oxalidaceae, lauraceae etc. The most commonly studied species are: *Trigonella foenum graecum, Momordica charantia, Ficus bengalensis* and *Gymnema sylvestre*. In the experiments, oral glucose tolerance test, streptozotocin and alloxan-induced diabetic mouse or rats were most commonly used model for the screening of antidiabetic drugs. Numerous mechanisms of actions have been proposed for plant extracts (Table 1). Some hypothesis relates to their effects on the activity of pancreatic beta cells, increase in the inhibitory effect against insulinase enzyme, increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may also be involved such as increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen or decrease of glycogenolysis, inhibition of intestinal glucose absorption [12].

In this review so many number of plants are included which have shown antidiabetic action through release of insulin and some extra pancreatic mechanisms [8]. Plants such as *Acacia Arabica, Aegla marmelos, Agrimony eupatoria, Aloe vera, Asparagus racemosus, Ficus bengalensis, Gymnema sylvestre, Momordica charantia, Pterocarpus marsupium* and *Syzygium cumini* have a great antidiabetic potential, which have already been subjected to the clinical trial are included in the list, whereas some marketed herbal formulations which have been proved for its antidiabetic activity are also listed in the database [16, 37]. Although all these plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity not all were effective in severe experimental diabetes and its related complications. A novel anti-hyperglycemic amino acid has been extracted and purified from fenugreek seeds (4-hydroxyleucine) which reportedly increases glucose-induced insulin release [10].

Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. However, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having antidiabetic effect [12].

Nanotechnology has great potential in the field of medicine today, so it is not hard to imagine that nanotechnology will become an important part of our lives tomorrow. Diabetic patients are able to survive for long time as equivalent to normal persons. The different approaches like Artificial Pancreas, Oral Insulin, Smart cell and Implantable sensor were new tools for treatment of diabetes, this methods has great credential in this field of treatment of disease like diabetes mellitus [50]. These applications take advantage of the unique

properties of nano particles as drugs or constituents of drugs or are designed for new strategies to controlled release, drug targeting, and salvage of drugs with low bioavailability (Table 2).

6. CONCLUSION

The systematic review clearly indicates that the herbal plants have hypoglycaemic activity and even they reduces the secondary complications of diabetes mellitus with minimal or no side effect. The review also reveals that the new approach of Nanotechnology for treatment of diabetes mellitus has futuristic scope. They have advantage over conventional method of treatment by its unique properties like nano-particles, as drugs or constituents of drugs are designed for controlled release, drug targeting, and salvage of drugs with low bioavailability. Hopefully, these new kind of treatment may help in making the everyday lives of millions of diabetes patients more comfortable.

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Conflict of interest

We declare that we have no conflict of interest.

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