On Anti-Diabetic Potential of Phyto-nanoparticles Comparison with Hormonal Therapy and Medicinal Plants

Amarvani P Kanjikar

Department of Biotechnology, Biopharmaceutical, and Nanobiotechnology, Gulbarga University, Kalaburagi, India.

ABSTRACT

In the last few years, there has been exponential growth in the field of herbal medicine in both developing and developed countries because of their natural base without side effects. A comprehensive review was conducted to collect data about how to combine medicinal plants with nanotechnology for the treatment of diabetes mellitus instead of hormonal treatments. Diabetes mellitus (DM) is a metabolic disorder, currently associated with morbidity, mortality and many long term complications in diabetic patients. Hyperglycemia is due to the insulin resistance or insufficient secretion of insulin. In India, the percentage of diabetes mellitus cases is rapidly increasing and at present, more than 40 million people have been affected i.e. it accounts for almost 20% of the total diabetic population worldwide. Treatment of the DM patients was achieved by the use of oral hypoglycemic/antihypoglycemic agents and insulin. However, all these treatments have limited efficacy and have been reported with side effects. In order to overcome this problem, the researchers have been shifted to the use of other alternative medicines. Folkal or traditional medicines and extracts from different parts of medicinal plants have been extensively used as alternative medicines to control and manage diabetes mellitus. Nanotechnology can be defined as the science and engineering involved in the synthesis, design, characterization, monitoring, repairing, construction and control of the human biological system at the molecular level. Nanomedicine is the integration of nanotechnology in medicine for better human health care. Nanomaterials have unique physicochemical properties, such as high surface to mass ratio, ultra-small size, and high reactivity. These properties can be used to overcome the limitations of traditional DM treatments and diagnosis.

Key Words: *Diabet, hormonal treatments, nanotechnology.*

eIJPPR 2019; 9(1):103-111

HOW TO CITE THIS ARTICLE: Amarvani P Kanjikar (2019). "On Anti-Diabetic Potential of Phyto-nanoparticles Comparison with Hormonal Therapy and Medicinal Plants", International Journal of Pharmaceutical and Phytopharmacological Research, 9(1), pp.103-111.

INTRODUCTION

Diabetes mellitus

International Diabetes Federation has estimated that the population of diabetic people will rise from 285 million, contributing 6.4% of the world adult population in 2010, to 438 million in 2030. India has been declared as the capital of diabetes in the world. Currently, 40.9 million people in India suffer from DM and in 2030 this number may increase to 79.44 million [1]. Diabetes mellitus is a syndrome which is characterized by hyperglycemia, caused a decrease in the production of insulin by pancreatic islet cells, leading to an increase in the level of blood glucose [2]. Diabetes insipidus is a condition characterized by the excretion of a large amount of urine, which cannot be reduced when fluid intake is reduced. This is due to antidiuretic hormone (ADH) also known as vasopressin which is secreted by the posterior pituitary gland. The symptoms of diabetes include weight loss, polyuria (excess urine), polydipsia (thirst) and polyphagia (excessive food) [3]. There are 3 major types of diabetes: Type 1 or insulin-dependent diabetes (T1DM), Type 2 or diabetes mellitus (T2DM) known as non-insulin-dependent diabetes mellitus (NIDDM) and gestational diabetes [4]. T1DM is characterized by a deficiency in insulin production and in children, it is termed as juvenile diabetes. T2DM is caused by insulin resistance or reduced

Corresponding author: Amarvani P Kanjikar
Address: Department of Biotechnology, Biopharmaceutical, and Nanobiotechnology, Gulbarga University, Kalaburagi, India.
E-mail: ✉ amarvanipkanjikar1989 @ gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .
Received: 05 November 2018; **Revised:** 12 February 2019; **Accepted:** 22 February 2019

insulin sensitivity combined with reduced insulin secretion. There are many current drugs, available to treat diabetes by remodeling of insulin sensitivity, booming the insulin production and cutbacking the amount of glucose level in blood. The detrimental effect of drug treatment is not always adequate in balancing the normal level of blood glucose [5].

Available treatments for DM

Currently, there are many drugs/medicines for treatment of diabetes mellitus, like:

1. Non-hormonal treatment
2. Hormonal treatment
3. Medicinal plants
4. Nano-particles

Non-hormonal treatment

There are many challenges in managing diabetes especially T2DM by nonhormonal drugs and also these drugs have side effects. Seven types of commonly used nonhormonal anti- hyperglycemic drugs recently remedy for the treatment of diabetes: sulfonylureas, glitazones, biguanides, alpha-glucosidase inhibitors (AGIs), meglitinides, sodium-glucose cotransporter inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Table 1 contains the nonhormonal antidiabetes therapeutic agents and side effect of these agents, respectively.

Table 1. The antidiabetes therapeutic agents and their side effects

Antidiabetes agent	Side effects	Limitation
Sulfonylureas	Allergy, weight gain, and hypoglycemia	Renal failure, hepatic failure, porphyria, pregnancy, and lactation
Biguanides	Gastrointestinal disturbance, lactic acidosis, And B12 deficiency	Chronic kidney diseases, pulmonary insufficiency and congestive cardiac Failure
Alpha-glucosidase inhibitors (AGIs)	Flatulence, diarrhea, and abdominal pain	Inflammatory bowel disease, renal And liver diseases, pregnancy and and lactation
Sodium-glucose co-transporter inhibitors	Genital mycotic infections, urinary tract infections, polyurea, hypotension, Hyperkalemia, increased LDL cholesterol	Renal diseases, pregnancy and lactation.
Dipeptidyl peptidase-4(DPP-4) inhibitors	Nausea, vomiting, diarrhea, nasopharyngitis, and pancreatitis.	Hypersensitivity reaction, history of pancreatitis and renal failure.

Alpha-glucosidase inhibitors (AGIs)

AGIs are the enzymes, which inhibit disaccharides by breaking them down into monosaccharides in the intestinal brush border and decrease the glucose level in the body [6]. AGIs have some limitations such as gastrointestinal side effects including flatulence, abdominal bloating and cramping. Due to these effects, many of the patients are unable to tolerate, and stop taking medicines.

Biguanides

Metformin is the most commonly used first-line oral nonhormonal treatment which is specially prescribed for T2DM. About 20-30% of diabetics withdrew from taking this drug due to its gastrointestinal-related side effects in certain conditions like renal failure, acute illnesses, and dehydration, causing lactic acidosis [7]. Therefore, the patient must be educated and aware of the illness condition to avoid the complications.

DPP-4 inhibitors

DPP-4 inhibitors stimulate beta cells to release glucose-dependent insulin and even inhibit the hepatic gluconeogenesis and decrease the glucagon secretion. Animal studies about DPP-4 suggested that they enhance the viability of pancreatic beta cells by inhibiting apoptosis, a process of natural cell death [8]. These agents are used as monotherapy or synergic with other oral drugs and insulin. The related side effects of these drugs include abdomen pain, nausea, vomiting, and anorexia [9].

Sodium-glucose cotransporter (SGLT2) inhibitors

Sodium-dependent glucose cotransporter (or sodium-glucose-linked transporter 2, SGLT2) is a group of glucose transporters synthesized in the proximal convoluted tubules from which 90% of glucose is absorbed. Dapagliflozin, canagliflozin, and empagliflozin are the currently available drugs in the market [10, 11].
These drug-related side effects are urine tract infection, genital mycotic infection, and related increased urination and episodes of hypotension and hyperkalemia.

GLP-I analog

GLP-1 is a peptide hormone, which is secreted by L cells of the small intestine and leads to glucose-dependent insulin release. Once circulated in the body, GLP-1 is rapidly degraded by the enzyme DDP-4, because it has a half-life of 1-2 minutes and it is immediately cleared by the kidney. This natural peptide hormone i.e. GLP-1 cannot be used for treatment, and GLP-1 receptor agonists are manufactured to bypass enzymatic degradation. There are two types of GLP-1 receptor agonists to treat T2DM: exenatide and liraglutide which are administered subcutaneously. Artificially synthesized GLP-1 has a mechanism similar to natural GLP-1 [12]. GLP-1 receptor agonists are very effective in reducing fasting as well as glucose excursion, and their combination with oral or basal insulin boost their effect [13]. Diabetic patients, using GLP-1 may suffer from nausea and vomiting. Taking liraglutide stimulates the C-cell hyperplasia and causes medullary thyroid carcinoma in rats [14].

Insulinization

Insulin therapy is not considered as the last treatment option, rather it should be preferred early in the treatment course of the disease. Early insulinization therapy helps the patient to achieve long term glycemic control and good quality of life, leads to rapid reversibility of glucolipotoxicity, decreases the inflammatory markers and cardiovascular risk. The patients on insulin therapy, achieve normoglycemia faster than the ones with oral therapy [15, 16].

Conventional human insulin (CHI) VS analog insulin

Beta cells of the pancreas secrete insulin to maintain the glucose level in blood. It releases in two phases, firstly release by carbohydrate as a meal characterized by quick first-phage release followed by slower second phase release. CHI may not mimic the similar pharmacokinetics of analog insulin physiologically stimulating the normal/natural insulin pharmacokinetic profile. Human insulin takes at least 30 minutes for absorbance from subcutaneous tissue and peaks after 2 hours. The conventional basal Neutral Protamine Hagedorn (NPH) insulin has different rates of absorption through the subcutaneous tissue and its action takes place in less than 24 hours, resulting in fast hyperglycemia and nocturnal hypoglycemia [17-19].

- Insulin therapy has many side effects, and hypoglycemia is the most common and serious complication about it [20].
- Weight gain is the most common problem in insulin-treated patients and it is most commonly linked to the conventional insulin than the analogs [21].

Future research for hormonal treatment

As a future potential hormone therapy for diabetes mellitus, Betatrophin is a key hormone to stimulate beta-cells in response to insulin resistance and obesity in mice. These findings are generated interest in the synthesis and development of antidiabetic drugs with betatrophin as an active agent [22] and it may cure the diabetics in the future.

Leptin is a hormone secreted by fat cells. The main function of this hormone is to maintain the amount of fats stored in the body by adjusting both sensations of hunger and energy expenditure. When hunger is eliminated, leptin is secreted and circulated throughout the body and activates the leptin receptors in the nucleus of the hypothalamus. Leptin gene therapy in rat model shows an effective result in not only glucose tolerance in both T1 and T2DM but also decreasing obesity and improving triglycerides [23, 24].

Ghrelin is a peptide hormone, secreted from neuroendocrine ghrelin cells in the gastrointestinal tract and its function is to regulate hunger and energy balance. Gherlin is produced when the stomach is empty and when the stomach is full of food contents, its production is stopped. Pharmaceutical companies are trying to develop drugs that can target orexigenic or obesity-related functions of ghrelin and its receptor [25]. More studies are needed to determine the efficacy, safety, and clinical indications to treat diabetes and obesity in the future.

Medicinal plants

Medicinal plants are good sources of health-related therapeutic aids to treat diseases. Strong traditional medicine systems such as Unani, Chinese, and Ayurvedic systems have been born and practiced over the 2500 years, especially in the eastern continent. 80 % of the people in developing countries prefer the medicines of these traditional systems for their primary health treatment [26]. The Indian Vedic literature like Charak Samhita reports the applications of medicinal herbs, plants, and their derivatives and extracts for diabetes mellitus treatment. Over 400 plants are identified against diabetes mellitus treatment in two third of the population around the world. There are many in vivo studies, already reported in various journals that have tested the hypoglycemic properties of plants on the animals [27, 28].

The plant family species, contributing to the management of hypoglycemic effects include Leguminoseae, Lamiaceae, Asteraceae, Rosaceae, Cucurbitaceae, Moraceae, Araliaceae and Euphorbiaceae.

Antidiabetic properties of plants

Azadirachta indica (Neem) is a large evergreen tree found all over India. The studies suggested that 200 mg/kg of the nimbidin seeds can reduce the blood glucose in alloxan-diabetic rabbits. The aqueous extract of tender leaves could potentially reduce the blood glucose level [29]. *Ficus bengalensis* known as banyan tree in English; is a large tree with aerial roots, found in all over India. A study conducted on alloxan diabetics rabbits and rats, as well as on diabetic people revealed that the bark of banyan can efficiently improve diabetes [30-32].

Pterocarpus marsupium (Roxb) is called as Indian Malabar in English and vijaysar in Hindi. It is a very large deciduous tree, 30 meters high found in hilly areas. Administration of the active compound, epicatechin, isolated from the ethanolic extract of bark, helps in lowering the blood glucose level of diabetic rats to near normal in hyperglycemic condition [33, 34]. *Catharanthus roseus* commonly called as *Vinca rosea L.*, has antidiabetic properties when the alcoholic extract of the plant is given to the streptozotocin-induced diabetic rats and shows a remarkable effect in lowering of glycemia in both diabetic and normal rats [35]. The leaf of *Bougainvillea spectabilis* has hypoglycemic property. Pinitol is the compound isolated from the leaves of this plant and has a significant hypoglycemic effect in diabetic

and normal mice [36]. *Coccinia indica* known as kanduri in Hindi, grows in the state of Bengal and other parts of India. The ethanolic extract of this plant has reputational status in Bengal to reduce the glucose level in the urine of diabetes mellitus patients [37]. Mangifera indica (Mango) has an antidiabetic property used in the treatment of diabetes mellitus and the aqueous extract of its leaves has a good hypoglycaemic effect compared with the oral dose of chlorpropamide [38]. *Cyamopsis tetragonolobus* (India cluster bean) contains antidiabetic principle [39].

Table 2: The names of the medicinal plants, their family and activity studied for hypoglycemic activity.

SI	plant name	family	activity	Reference
01	*Cocos nucifera L*	Arecaceae	Antidiabetes activity	[40]
02	*Aloe vera Indian Aloe Ghikanvar*	Liliaceae	NIDDM patients	[41]
03	*Allium sativum*	Liliaceae	Diabetic rabbits	[42]
04	*Anemarrhena asphodeloides*	Liliaceae	Diabetic mice	[43]
05	*Allium cepa*	Liliaceae	Diabetic rat	[44]
06	*Phyllanthus amarus*	Euphorbiaceae	Diabetic patients	[45]
07	*Asteracantha longifolia*	Acanthaceae	Diabetic patients	[46]
08	*Bombax ceiba*	Bombacaceae	Rats	[47]
09	*Solanum verbascifolium*	Solanaceae	Diabetic rabbit	[48]
10	*Spinacea oleracea L*	Solanaceae	Rabbit	[49]
11	*Bouvardia ternifolia*	Rubiaceae	Diabetes mice	[50]
12	*Ocimum sanctum*	Limiaceac	Antidiabetes	[51]
13	Opuntia streptacantha	Cactaceae	Antihyperglycemic	[52]
14	Albizia odoratissima	Mimoaceae	Antidiabetes	[53]
15	Brassica juncea	Cruciferae	Hypoglycemic	[54]
16	Zygophyllum album	Zygophyllaceae	Antidiabetes	[55]
17	Vitex negundo	Lamiaceae	Antihyperglycemic	[56]
18	*Acacia Arabica*	Fabaceae	Antidiabetes	[57]
19	*Psidium guajava*	Myrtaceae	Antidiabetes	[58]
20	*Bryophyllum pinnatum*	Crassulaceae	STZ rat	[59]
21	*Canarium schweinfurthii*	Burseraceae	STZ rat	[60]
22	*Hintonia standleyana*	Rubiaceae	STZ rat	[61]
23	*Annona squamosa*	Annonaceae	STZ rat	[62]
24	*Momordica charantia*	Cucurbitaceae	STZ mice	[63, 64]
25	*Coscinium fenestratum*	Menispermaceae	STZ rat	[65]

Recent trends in the treatment of diabetes by using nanotechnology

The present article discusses the potentiality and application of BioMEMS, polymeric nanoparticles, and oral insulin administration using polysaccharides as insulin delivery systems for diabetes treatment. There are a few limitations in the use of conventionally available drug delivery systems for treatment of diabetes including the diminished potency due to drug metabolism in the body, nonspecificity of the target, and altered effects. Biocompatible nanoparticles with optimized physical, chemical, and biological properties can overcome these limitations with effective drug delivery systems. These modern drug delivery system generations have significant advantages in comparison to conventional drug delivery systems. This review also discusses the need for nanoparticulate drug delivery systems, their limitations, advantages, and recent advances in their application in diabetes treatment.

Nanoparticles for insulin delivery

There are many types of currently available nanoparticles that are studied for their uses as drug delivery systems, as follows [66].

- Ceramic nanoparticles
- Polymeric nanoparticles
- Liposomes
- Gold nanoparticles

The scientific community is working towards utilizing nanoparticle-based drug delivery systems in the treatment of diabetes-associated complications. The advantages and limitations of various types of nanoparticles are discussed in Table 3.

Table 3: Advantages and limitations for different types of nanoparticles

Types of nanoparticles	Advantages	Limitations
Polymeric nanoparticles	Degrade into biologically acceptable compounds by hydrolysis; lesser cytotoxicity; higher target-specificity; high level of insulin entrapment and ability to preserve insulin structure and biological activity; bypassing of the enzymatic degradation in the stomach	Mucoadhesive polymeric nanoparticles may adhere nonspecifically to the surfaces they are not intended to (gastric mucosa, gut content) or remain trapped within the mucus.
Ceramic nanoparticles	Easy preparative processes; high biocompatibility; ultra-low size (less than 50 nm); good dimensional stability; protect the doped drug molecules against denaturation caused by changes in external pH and temperature; can be manufactured with desired size, shape and porosity; do not undergo swelling or porosity changes	Poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism of non-mucoadhesive formulations for nasally administered insulin
Gold nanoparticles	Long term stability in terms of aggregation and good insulin loading; higher uptake of insulin across oral and nasal mucosa; improved pharmacodynamic activity of insulin	Widespread distribution in organs like liver, lung, spleen, kidney, brain, heart, stomach and joints
Liposomes	Biodegradable, non-toxic and non-immunogenic	Drug loading capacity remains inconclusive; captured by the human body's defense system (reticuloendothelial system (RES)); post-treatment accumulation in skin and eyes

Nanotechnology in relation to medicinal plants

Nanotechnology is knowing and controlling the matter generally in the range of 1-100 nm. The practice of nanotechnology in medicine is generally called as nanomedicine, which is the development of precise engineered materials at a smaller scale to innovate novel therapeutic and diagnostic modalities [67]. To prevent adverse side effects and to increase the drug bioavailability, it is required to use plant products for the synthesis of nanoparticles in the modern nanobiotechnology, named as phytonanoparticles [68, 69]. Phytonanoparticles have the potential advantage by developing the Novel Drug Delivery System (NDDS) for treatment of various diseases like diabetes mellitus, asthma, cancer, etc. [70, 71]. Green synthesis of nanoparticles is an emerging field of nanotechnology. Biosynthesis of nanoparticles by using the plant extracts is a popular method because the plants are widely distributed, easily available, advanced in comparison to the physical and chemical methods, safe with no side effects, eco-friendly, cost-effective, and no need to use toxic chemicals in the synthesis [72].

Solanum nigrum is a plant, which belongs to the Solanaceae family; many parts of the plant are used as traditional medicine. Due to this property, the plant was subjected to the synthesis of silver nanoparticles and reported the efficacy of S. nigrum mediated AgNPS as an anti-hyperglycemic activity on alloxan-induced diabetes rats [73, 74]. *Costus pictus* D, commonly called as spiral ginger, belongs to the family Cactaceae. It is known as an insulin plant, for a magical cure of diabetes mellitus. Leaves of this plant stimulate to build up insulin in the human body. In-vivo and in-vitro studies show the potential activity of the plant against the antidiabetic activity. The plant extract was used for the synthesis of silver nanoparticles against diabetes mellitus [75-77].

Dioscorea bulbifera Eng; Yam, belonging to the family Dioscoreaceae, is commonly found in India. The tuber has a significant activity such as antimicrobial, antihyperlipidemic, antitumor, and anti-inflammatory properties. Recently the synthesis of silver and gold nanoparticles with potent biological applications has been done on D. bulbifera [78, 79]. The plant extract has also been used to synthesize copper nanoparticles with a significant effect on anti-diabetic activity in in-vitro conditions [80]. Cassia fistula, a member of the Leguminosae family, has been used as Indian traditional medicine. The plant parts were used as medicine for the treatment of various diseases like anti-inflammatory, hepatoprotective, antitumor and antioxidant activity. The hexane bark extract of this plant had hypoglycemic and hypocholesterolemic activities [81, 82]. The efficacy of plants, chosen for the synthesis of gold-nanoparticles against streptozotocin-induced diabetic rat showed good recovery and had the promising agent against diabetes

mellitus and its associated complications [83]. Hibiscus sabdariffa L belongs to family Malvaceae and is commonly popular as Indian sorrel. This plant is commonly grown for the fiber and edible purposes and used as a native traditional medicine in India, Africa, and Mexico. The extract of the leaf and calyx of the plant found to have diuretic, hypotensive, blood pressure suppressive, antioxidant, antitumor and anticancer agents [84, 85]. The study also reported having effective antimicrobial and anti-diabetes mellitus agents [86]. H. sabdariffa extract was used to synthesis of ZnO nanoparticles as effective anti-diabetic drugs.

CONCLUSION

This review article had an attempt to review the treatment of diabetes mellitus by available drugs like hormonal, non-hormonal, medicinal plants, nanotechnology, and phyto-nanotechnology. Folklore medicinal plants are mostly used to treat diabetes mellitus in rural areas; because of the availability of a large number of medicinal plants in those areas. Uses of nonhormonal antidiabetic drugs carry risks, limitations, and side effects when prescribed in certain conditions in comparison to treatment with hormones like insulin and incretin-based hormonal therapy. In the present study, an attempt has been made to investigate the antidiabetic medicinal plants, which may be useful to the scientists, health professionals, and research scholar, working in the field of pharmacology and therapeutic development of anti-DM drugs. Technical and scientific aspects of nanomedicine in related to diabetes have high and potential benefits but the safety of nanomedicine is not yet clear. Nanomedicine shows great potential for future diabetes management and at the moment, the suggested benefits in diabetic healthcare. Here we concluded that the use of nanomedicine in diabetic patients is in the initial stages, but it is rapidly progressing. Diabetes treatment has various remaining problems; nanomedicine is likely to be an essential and key technology for solving many of them and will be a critical technology in diabetic research.

REFERENCES

[1] Singh, U., Kochhar, A., Singh, S.: Blood glucose lowering potential of some herbal plants. J. Med. Plants Res. 5(19), 4691–4695 (2011)
[2] Alvin, C.P., David Allesio, D.D.: Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycaemia. In: Brunton, L., Chabner, B., Knollman, B. (eds.) Goodman and Gilman's the Pharmacological Basis of Therapeutics, 12th edn, p. 1237. McGraw-Hill, New York (2011)
[3] Kuzuya, T.; Nakagawa, S.; Satoh, J.; Kanazawa, Y.; Iwamoto, Y.; Kobayashi, M.; Nanjo, K.; Sasaki, A.; Seino, Y.; Ito, C.; Shima, K.; Nonaka, K.; Kadowaki, T. Diabetes Res. Clin. Pract., 55(1), 65 (2002).
[4] Rao BK, Rao CH (2001) Hypoglycemic and antihyperglycemic activity of Syzygium alternifolium (Wt.) Walp. seed extracts in normal and diabetic rats. Phytomedicine 8: 88-93.
[5] Murali Mohan N. M.Sc Thesis entitled Biochemical studies on α- amylase inhibitors derived from Indian medicinal herbs as potential anti-diabetic agent submitted to Andhra University, Visakhapatnam 2006, 25-30.
[6] Lebowitz HE. Alpha-glucosidase inhibitors as agents in the treatment of diabetes. Diabetes Rev. 1998;6:132–145.
[7] Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case control analysis. Diabetes Care. 2008;31:2086–2091.
[8] Pospisilik JA, Stafford SG, Demuth HU. Long-term treatment with dipeptidyl peptidase IV inhibitor improves hepatic and peripheral insu¬lin sensitivity in the VDH Zucker rat: a euglycemic-hyperinsulinemic clamp study. Diabetes. 2003;51:2677–2683.
[9] Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2009;32: 834–838.
[10] Nair S, Joseph F, Ewins D, Wilding J, Goenka N. From history to reality: sodium glucose co-transporter 2 inhibitors – a novel therapy for type 2 diabetes mellitus. Pract Diabetes Int. 2010;27:311–316.
[11] List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009;32:650–657.
[12] Drucker DJ. Biologic actions and therapeutic potential of the proglucagon-derived peptides. Nat Endocrinol Metab. 2005;1:22–31.
[13] Peters A. Incretin-based therapies: review of current clinical trial data. Am J Med. 2010;123(Suppl):S28–S37
[14] Derosa G, Maffioli P. GLP-1 agonists exenatide and liraglutide: a review about their safety and efficacy. Curr Clin Pharmacol. 2012;7: 214–228.
[15] Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycemic control in patients with newly diagnosed type 2

diabetes: a multicentre randomized parallel-group trial. Lancet. 2008;371:1753–1760.

[16] Pfützner A, Lorra B, Abdollahnia MR, et al. The switch from sulfo¬nylurea to preprandial short-acting insulin analog substitution has an immediate and comprehensive β-cell protective effect in patients with type 2 diabetes mellitus. Diabetes Technol Ther. 2006; 8:375–384.

[17] Ritzel RA, Bulter PC. Physiology of glucose homeostasis and insu¬lin secretion. In: Leahy JL, Cefalu WT, editors. Insulin Therapy. New York, NY: Marcel Dekker; 2002:61–72.

[18] Hirsch IB. Insulin analogues. N Engl J Med. 2005;352:174–183.

[19] Holleman F, Gale E. Nice insulins, pity about the evidence. Diabetologia. 2007;50:1783–1790.

[20] Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–139.

[21] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia. 2008;51:408–416.

[22] Yi P, Park JS, Melton AD. Betatrophin: a hormone that controls pan¬creatic β cell proliferation. Cell. 2013;153(4):747–758.

[23] Brennan AM, Mantzoros CS. Drug Insight: the role of leptin in human physiology and pathophysiology – emerging clinical applications. Nat Clin Pract Endocrinol Metab. 2006;6:318–327.

[24] Cummings BP. Leptin therapy in type 2 diabetes. Diabetes Obes Metab. 2013;15(7):607–612.

[25] Zorrilla EP, Iwasaki S, Moss JA, et al. Vaccination against weight gain. Proc Natl Acad Sci U S A. 2006;103(35):13226–13231.

[26] Tsay HS, Agrawal DC. Tissue Culture Technology of Chinese Medicinal Plant Resources in Taiwan and their Sustainable Utilization. Int J App Sci Eng 2005; 3:215-223.

[27] A. Chauhan, P. K. Sharma, Plants Having Potential Antidiabetic Activity: A Review Der Pharmacia Lettre, 2010, 2(3): 369-387

[28] WL. Li, H. C. Zheng c, J., Bukuru b, N. De Kimpeb, Journal of Ethnopharmacology, 2004,92, 1–21.

[29] Pillai, N.R. and Santha Kumari, G. (1981) Hypoglycemic activity of Melia azadirachta. Ind. J. Med. 74, 931-933.

[30] Vohra, S.B. and Parasar, G.C. (1970) Antidiabetic studies on Ficus bengalensis Linn. Ind. J. Pharmacy 32, 68-69.

[31] Shukla, R., Anand, K., Prabhu, K.M. and Murthy, P.S. (1994) Hypoglycemic effect of the water extract of Ficus bengalensis in alloxan recovered mildly diabetic and severely diabetic rabbits. Internatl. J. Dia. Dev. Countries 14, 78-81.

[32] Joglekar, J.C., Shrotri, D.S., Aiman, R. and Balwani, J.H. (1963) A study on Ficus bengalensis Lin.,J. Ind. Med. Assoc. 40, 11-12.

[33] Dharmadhikari, SD., Patki, V.P. and Dasgupta, P.G.(1984) Study of mechanism of hypoglycemia due to Pterocarpus marsupium. Ind. J. Pharmacol. 16, 61.

[34] Chakraborty, B.K., Gupta, S. and Gode, K.D. (1982) Functional 13 cell regeneration in the islet of pancreas in atloxan induced diabetic rats by (-) epicatechin. Life Sci 31, 2693-2697.

[35] Benjamin BD, Kelkar SM, Pote MS, et al. Catharanthus roseus cell cultures: Growth, alkaloid synthesis and antidiabetic activity. Phytother Res 1994; 8: 185-186.

[36] Indian Medicinal Plants 1989, Eds. Ram P. Rastogi and B.N. Malhotra. Central Drug Research Institute, Lucknow, Council for Scientific and Industrial Research, Delhi, Vol. IV.

[37] Hossain, M.Z., Shibib, B.AI and Rahman, R. (1992) Hypoglycaemic effect of Coccinia indica. Inhibition of key gluconeogenic enzyme glucose 6 phosphatase. Ind. J. Exp. Biol. 30, 418-420.

[38] Aderibigebe AO, Emudianughe Lawal BA. Antihyperglycaemic effect of Mangifera indica in rat. Phytother Res 1999; 13: 504-507.

[39] Pillai, N.R., Seshadri, C. and Santhakumari, G. (1980) Hypoglycemic effect of Cyamopsis tetragonolob taub (Gowar). Ind. J. Med. Res. 72, 128-31.

[40] Sindurani JA, Rajamohan T. Effects of different levels of coconut fiber on blood glucose, serum insulin and minerals in rats. Indian J Physiol Pharmacol 2000; 44: 97-100.

[41] Alawadi, F.M., Katar, M.A. and Gumaa, K.A. (1985) On the mechanism ohypoglycemic effect of a plant extract. Dibetologia 28, 432-438.

[42] Roman-Ramos, R., Floreo Saenz, J.L. and Alarcon Aquilar, EJ. (1995) Antihyperglycemic effect of some edible plants. J. Ethanopharmacol. 48(1), 25-32.

[43] Takashaki, M., Kinno, C. and Hikino, H. (1985)Isolation and hypoglycaemic activity of Anemarans A, B, C and D glycans of Anemarrhena asphodeloides rhizomes. Planta Medica 51,100-102.

[44] Jain, R.C. and Vyas, C.R. (1974) Hypoglycemic action of onion on rabbits. Brit. Med. J. 2, 730.
[45] Srividya, N. and Perimal, S. (1995) Diuretic, hypotensive and hypoglycemic effect of Phyllanthus amarus. Ind. J. Exp. Biol. 33,861-864.
[46] Fernando MR, Wickramasinghe N, Thabrew MI, Ariyananda PL, Karunanayake EH. Effect of Artocarpus heterophyllus and Asteracanthus longifolia on glucose tolerance in normal human subjects and in maturity-onset diabetic patients. J Ethnopharmacol 1991; 31: 277-282
[47] Saleem R, Ahmad M, Hussain SA, et al. Hypotensive, hypoglycaemic and toxicological studies on the flavonol C-glycoside shamimin from Bombax ceiba. Planta Med 1999; 65: 331-334.
[48] Roman-Ramos R, Flores-Saenz JL, Partida-Hernandez G. Experimental study of the hypoglycaemic effect of some antidiabetic plants. Arch Invest Med (Mex) 1991; 22: 87-93.
[49] Roman-Ramos R, Flores-Saenz JL, Alarcon-Aguilar F. Antihyperglycaemic effect of some edible plants. J Ethnopharmacol 1995; 48: 25-32.
[50] Perez-Gutierrez RM, Perez-Gonzalez C, Zavala-Sanchez MA, Perez-Gutierrez S. Hypoglycaemic activity of Bouvardia terniflora, Brickellia veronicaefolia, and Parmentiera edulis. Salud Publica Mex 1998; 40: 354-358.
[51] Patil R, Patil R, Ahirwar B, Ahirwar D. Isolation and characterization of anti-diabetic component (bioactivity guided fractionation) from Ocimum sanctum L. (Lamiaceae) aerial part. Asian Pac J Trop Med 2011; 278-282
[52] Cetto AA, Wiedenfeld H. Anti-hyperglycemic effect of Opuntia streptacantha Lem. J Ethnopharmacol 2011; 133: 940-943.
[53] Kumar D, Kumar S, kohli S, Arya R, Gupta J. Antidaibetic activity of methanolic bark extract of Albizia odoratissima Benth in alloxan induced diabetic albino mice. Asian Pac J Trop Med 2011; 4: 900-903.
[54] Thirumalai T, Therasa VS, Elumalai EK, David E. Hypoglycemic effect of Brassica juncea (seeds) on streptozotocin induced diabetic male albino rat. Asian Pac J Trop Biomed 2011; 4: 323-325.
[55] Ghoul JE, Boughanmi NG, Attia MB. Biochemical study on the protective effect of ethanolic extract of Zygophyllum album on streptozotocin induced oxidative stress and toxicity in mice. Biomed Preventive Nutr 2011; 1(2): 79-8
[56] Sundaram R, Naresh R, Shanthi P, Sachdanandam P. Antihyperglycemic effect of iridoid glucoside, isolated from the leaves of Vitex negundo in streptozotocininduced diabetic rats with special reference to glycoprotein components. Phytomedicine 2012; 19(3-4): 211-216.
[57] Nojima H, Kimura I, Chen FJ, Sugihara Y, Haruno M, Kato A, et al. Antihyperglycemic effects of Ncontaining sugars from Xanthocercis zambesiaca, Morus bombycis, Aglaonema treubii, and Castanospermum australe in streptozotocin-diabetic mice. J Nat Prod 1998; 61(3):397-400.
[58] Ojewole JA. Hypoglycemic and hypotensive effects of Psidium guajava Linn. (Myrtaceae) leaf aqueous extract. Methods Findings Experiment Clin Pharmacol 2005d; 27:689-695.
[59] Kamtchouing P, Kahpui SM, Dzeufiet PD, Tedong L, Asongalem EA, Dimo T. Anti-diabetic activity of methanol/methylene chloride stem bark extracts of Terminalia superba and Canarium schweinfurthii on streptozotocin-induced diabetic rats. J Ethnopharmacol 2005; 104:306-309.
[60] Ojewole JA. Antinociceptive, anti-inflammatory and antidiabetic effects of Bryophyllum pinnatum (Crassulaceae) leaf aqueous extract. J Ethnopharmacol 2005a; 99:13-19.
[61] Navarrete A, Mata R. Antihyperglycemic effect of constituents from Hintonia standleyana in streptozotocin-induced diabetic rats. Planta Medica 2005; 71:1099-1105.
[62] Gupta RK, Kesari AN, Murthy PS, Chandra R, Tandon V, Watal G. Hypoglycemic and antidiabetic effect of ethanolic extract of leaves of Annona squamosa L. in experimental animals. J Ethnopharmacol 2005a; 99:75-81.
[63] Basch WE, Gabardi S, Ulbricht C. Bitter Melon (Momordica charantia): A Review of Efficacy and Safety. Am J Health-Syst Pharm 2003; 60(4):356-359.
[64] Sekar DS, Sivagnanam K, Subramanian S. Antidiabetic activity of Momordica charantia seeds on streptozotocin induced diabetic rats. Pharmazie 2005; 60:383-387.
[65] Shirwaikar A, Rajendran K, Punitha IS. Antidiabetic activity of alcoholic stem extract of Coscinium fenestratum in streptozotocin-nicotinamideinduced type 2 diabetic rats. J Ethnopharmacol 2005; 97:369-374.
[66] Attivi, D.; Wehrle, P.; Ubrich, N.; Damge, C.; Hoffman, M.; Maincent, P. Drug. Dev. Ind. Pharm. 31(2), 179 (2005).
[67] Farokhzad, O.C. & Langer, R. Nanomedicine: developing smarter therapeutic and diagnostic modalities. Adv. Drug Deliv. Rev. 58, 1456–1459 (2006).
[68] Shanmugavel S, Karthikeyan V. Synthesis and characterization of layer by layer magnetic

nanoparticles of Methotrexate and Melphalan. World J Pharm. Pharm. Sci., 2013; 3(2): 1809-24.

[69] Surendiran A, Sandhiya S, Pradhan SC, Adithan C. Novel applications of nanotechnology in medicine. Ind J Med Res., 2009; 130 (6): 689-701.

[70] Vimalanathan AB, Tyagi V, Rajesh A, Devanand P, Tyagi MG. Biosynthesis of silver nanoparticles using Chinese white ginseng plant root Panax ginseng. World J Pharm. Pharm. Sci, 2013; 2(5): 2716-25.

[71] Yadav D, Suri S, Chowdhary AA, Sikender M, Hemant, Beg NM. Novel approach: Herbal Remedies and Natural Products in Pharmaceutical Sciences as nano drug delivery systems. Int J Pharm Tech. 2011; 3: 3092-4116.

[72] Roy N and Barik A. Green synthesis of silver nanoparticles from unexploited weed resources. Int. J. Nanotech and Appl.2001; 4 (2): 95-101.

[73] Jain, R., Sharma, A., Gupta, S., Sarethy, I.P., Gabrani, R.: Solanum nigrum: current perspectives on therapeutic properties. Altern. Med. Rev. 6, 78–85 (2011).

[74] Arumugam Sengottaiyan, Adithan Aravinthan, Chinnapan Sudhakar. Synthesis and characterization of Solanum nigrum-mediated silver nanoparticles and its protective effect on alloxan-induced diabetic rats. J Nanostruct Chem (2016) 6:41–48

[75] Jose B, Reddy LJ. Analysis of the essential oils of the stems, leaves and rhizomes of the medicinal plant Costus pictus from Southern India. Int J Pharmacy Pharm Sci. 2010; 2 (Suppl 2): 100–1.

[76] Mani P, Kumar AR, Bastin TM, Jenifer S, Arumugam M. Comparative evaluation of extracts of C. igneus (or C. pictus) for hypoglycemic and hypolipidemic activity in alloxan diabetic rats. Int J Pharm Tech. 2010; 2: 183–95.

[77] Ajithadas Aruna, Ramraj Nandhini, Venkatachalam Karthikeyan, Pandi Bose. Synthesis and Characterization of Silver Nanoparticles of Insulin Plant (costus pictus d. don) Leaves. Asian Journal of Biomedical and Pharmaceutical Sciences; 04 (34); 2014; 1-6.

[78] Ghosh S, Parihar VS, More P, Dhavale DD, Chopade BA (2015) Phytochemistry and therapeutic potential of medicinal plant: Dioscorea bulbifera. Med Chem (Los Angeles) 5: 154-159.

[79] Ghosh S, More P, Derle A, Patil AB, Markad P, et al. (2014) Diosgenin from Dioscorea bulbifera: novel hit for treatment of type II diabetes mellitus with inhibitory activity against Î±-amylase and Î±-glucosidase. PLoS One 9: e106039.

[80] Ghosh S, More P, Nitnavare R, Jagtap S, Chippalkatti R, et al. (2015) Antidiabetic and Antioxidant Properties of Copper Nanoparticles Synthesized by Medicinal Plant Dioscorea bulbifera. J Nanomed Nanotechnol S6: 007. doi:10.4172/2157-7439.S6-007.

[81] Gupta RK. Medicinal and Aromatic Plants. 1st ed. New Delhi: CBS Publishers and Distributors; 2010.

[82] Nirmala A, Eliza J, Rajalakshmi M, Edel P, Daisy P. Effects of hexane extract of Cassia fistula barks on blood glucose and lipid profile in streptozotocin diabetic rats. Int J Pharmacol. 2008;4:292–296.

[83] P Daisy, K Saipriya. Biochemical analysis of Cassia fistula aqueous extract and phytochemically synthesized gold nanoparticles as hypoglycemic treatment for diabetes mellitus. International Journal of Nanomedicine 2012:7 1189–1202

[84] A. Sharaf, The pharmacological characteristics of Hibiscus sabdariffa L, Planta Med., 1962, 10, 48–52.

[85] E. Jim´enez-Ferrer, J. Alarc´on-Alonso, A. Aguilar-Rojas, A. Zamilpa, et al. Diuretic effect of compounds from Hibiscus sabdariffa by modulation of the aldosterone activity, Planta Med., 2012, 78(18), 1893–1898.

[86] Niranjan Bala S. Saha M. Chakraborty M. Maiti S. Green synthesis of zinc oxide nanoparticles using Hibiscus subdariffa leaf extract: effect of temperature on synthesis, anti-bacterial activity and anti-diabetic activity. RSC Adv., 2015, 5, 4993.