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Nanotechnological approaches for the development of herbal drugs in treatment of diabetes mellitus – a critical review

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Abstract: Diabetes mellitus (DM) is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. The number of people with diabetes is increasing due to population growth, ageing, urbanisation and increasing prevalence of obesity and physical inactivity. Apart from currently available therapeutic options, many herbal medicines have been recommended for the treatment of diabetes. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost. Several pharmacopoeias have provided parameters to maintain quality and standardise procedures in identification/authentication of herbal inputs and their products. Available literature related to folklore medicine used in the treatment of diabetes extended to nanoformulation of herbal drugs up to date was cited. The use of bioactive compounds leads to new hope to improve the life expectancy and health status of the population for the formulation of novel drugs. Recently, many studies have shown that nanotechnology has the potential to be used in different biological and medical applications, mainly as targeted drug delivery systems to minimise and delay the chronic effects of diabetes. Herein, the authors presented a thorough review of the available herbal medicines and the possibilities of developing their nanoformulations in the treatment of DM.

1 Introduction

Diabetes mellitus (DM) is characterised by hyperglycaemia besides leading to many complications such as hyperlipidaemia, hyperinsulinaemia, obesity, atherosclerosis and even cardiovascular disease [1]. Severe hyperglycaemia includes polyuria, polydipsia, polyphagia, weight loss and blurred vision. It is a syndrome characterised by hyperglycaemia, altered lipid metabolism [2] and is a condition where the body fails to use the consumed glucose properly, which could be due to lack of the hormone insulin or because the insulin that is available is not working effectively. Deficient insulin action on target tissues is the basis of abnormalities in carbohydrate, fat and protein metabolism in diabetes.

DM is a chronic, lifelong condition that affects body's ability to use the energy found in food and classified into four broad types, i.e. type 1 (T1DM), type 2 (T2DM), gestational diabetes (GDM) and 'other specific types' [3], and is schematically represented in Fig. 1. Improvement in the insulin sensitivity or reduction in hepatic glucose production can overcome the condition of hyperglycaemia (Fig. 2). Genetics and lifestyle of an individual are preliminary causes for T2DM and moreover smoking, hypertension and hyperlipidaemia are other factors that contribute to the development of peripheral artery disease in diabetics [4]. GDM complicates the pregnancy and the problems like altered duration of pregnancy, placental failure, hypertension/pre-eclampsia and high birth weight of the newborn may develop with GDM. In addition to these types, DM is classified under 'other specific types'. The common categories of secondary diabetes to consider in clinical practice are monogenic diabetes, exocrine pancreatic pathology, other endocrine disease and the unwanted effects of medications.

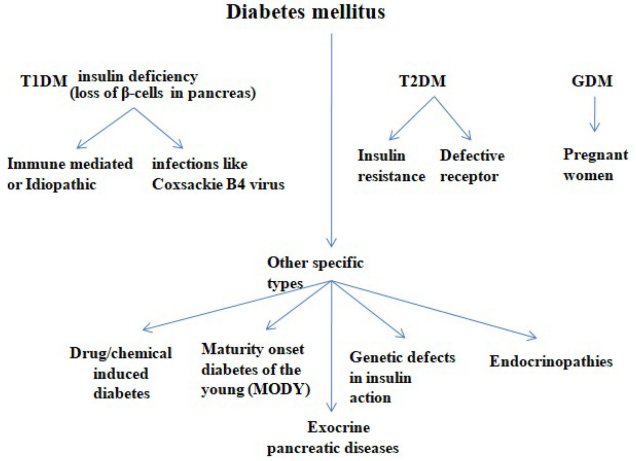

Fig. 1 *Classification of DM*

1.1 Prevalence and complications of DM

DM is the most common metabolic disorder affecting more than 200 million people worldwide. It has been estimated that the global burden of T2DM for 2010 would be 285 million people, which is projected to increase to 438 million in 2030 [5]; a 65% increase. Mortality attributable to DM accounts for 2–3% of deaths in poor countries and over 8% in the USA, Canada and the Middle East. In people 35–64 years old, 6–27% of deaths are attributable to DM. Approximately 7% of the people worldwide, in the age group 20–79 years, is estimated to have DM in 2010. This number is expected to rise by more than 50% in the next 20 years. This number is expected to rise by more than 50% in the next 20 years. Similarly, for India this increase is estimated to be 58%, from 51 million people in 2010 to 87 million in 2030 [5].

Diabetic complications are majorly grouped into two types – acute and chronic [6].

1.1.1 Acute complications:

- *Diabetic ketoacidosis (DKA)* is an acute and dangerous complication. Low insulin levels cause the liver to turn fatty acid to ketone for fuel (i.e. ketosis). Ketoacidosis can easily become severe enough to cause hypotension, shock and death. Urine analysis will reveal significant levels of ketone bodies

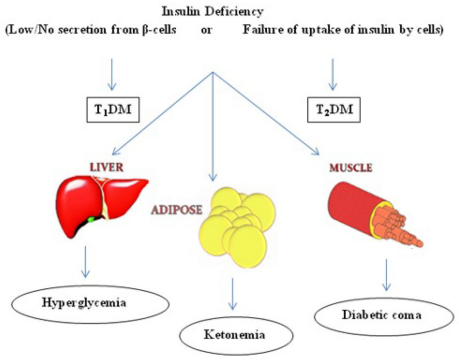

Fig. 2 *Metabolism in brief during diabetes*

(which have exceeded their renal threshold blood levels to appear in the urine, often before other overt symptoms).

- *Hyperglycaemia hyperosmolar state* is a condition with very high [usually considered to be above 300 mg/dl (16 mmol/l)] blood glucose levels where water is osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine. This results in loss of water and an increase in blood osmolarity. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels, combined with the loss of water, will eventually lead to dehydration.
- *Hypoglycaemia state makes the* patient agitated, sweaty, weak, and has many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilised panic. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death.
- *Diabetic coma* is a situation in which a person with DM is comatose (unconscious) may be because of severe diabetic hypoglycaemia, advanced DKA, extreme hyperglycaemia and dehydration.
- *Respiratory infections* such as pnuemonia and influenza due to hyperglycaemia by reducing the function of immune cells and increases inflammation.
- *Periodontal disease is a gum* disease, frequently related to bacterial infection by organisms such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetem comitans*.

1.2 Treatment of DM

Many of the drugs available in the market are associated with one or more side effects and hence treatment for DM makes this disease a major health problem around the world. The search for effective drugs for the treatment of DM with less or no side effects is continuing.

The major components of the treatment of diabetes are:

Diet (combined with exercise if possible) [7]:

Diabetics should focus on:

- weight control
- nutritional requirements allowing good glycaemic control with blood glucose levels as close to normal as possible
- correcting any associated blood lipid abnormalities
- antihyperglycaemic drugs

Oral hypoglycaemic drug therapy [8]: These are considered only when dietary treatment combined with exercise has failed to achieve the target results.

Biguanides (metformin): Its primary mechanism of action is suppression of hepatic glucose output and affects primarily on fasting glycaemia. The most common side effects are gastrointestinal complaints, such as diarrhoea, nausea, abdominal discomfort and a metallic taste.

Thiazolidinediones: These are agonists of peroxisome proliferator-activated receptor gamma and they primarily enhance the sensitivity of muscle and fat and mildly of the liver, to exogenous and endogenous insulin. Major side effects include weight gain, with an increase in subcutaneous adiposity, and fluid retention, which typically manifests as peripheral oedema, but heart failure has been shown to occur on occasion.

Sulphonylureas: They inhibit efflux of K+ from pancreatic ß-cells leading to depolarisation of the ß-cell membrane and, as a consequence, voltage-dependent Ca++ channels on the ß-cell membrane then open to permit entry of Ca++. The resultant increased binding of Ca++ to calmodulin results in activation of kinases associated with endocrine secretory granules thereby promoting the exocytosis of insulin-containing secretory granules. The main adverse effects include weight gain and hypoglycaemia.

Alpha glucosidase inhibitors: These competitively block the enzyme alpha glucosidase in the brush borders of the small intestine, which delays absorption of carbohydrates (absorbed in the mid and distal portions of the small intestine instead). They primarily target postprandial hyperglycaemia without causing hypoglycaemia. Gastrointestinal complaints, such as bloating, abdominal cramps, flatulence and diarrhoea are the main side effects.

Exenatide: It mimics glucagon-like peptide type-1 (GLP-1). GLP-1 is produced in the small intestine, which stimulates insulin secretion and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner. The major side effects are gastrointestinal complaints such as nausea, vomiting and diarrhoea.

Dipeptidyl peptidase 4 (DPP 4) inhibitors: DPP 4 is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide. Suppression of DPP 4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner. The most common side effect is headache and at times increase in nasopharyngitis.

Pramlintide: It is a synthetic form of amylin, a hormone secreted by beta-cells that acts to suppress glucagon secretion, slow gastric emptying, and suppress appetite through central pathways. It acts primarily on postprandial blood glucose levels. The major side effects are gastrointestinal complaints, especially nausea and hypoglycaemia.

Bromocriptine: It is a central dopamine agonist and when given in rapid-release form in the morning within 2 h of awakening it improves glycemic control in patients with T2DM.

Insulin treatment: Insulin is the oldest medical therapy available for diabetes. Insulin therapy is not the first-line treatment for T2DM and usually follows on from the failure of standard oral agents or other injectable therapies. Due to the progressive nature of T2DM, characterised by beta cell dysfunction and impairment, over time most patients with T2DM fail to reach their individualised HbA1c targets. Thus, many people with T2DM need to include insulin in their treatment to maintain glucose control and slow down the progression of diabetes complications.

Treatment with insulin remains essential for the management of T1DM [9] via either subcutaneous injections or continuous subcutaneous insulin infusion using a pump worn 24 h per day. The aim of exogenous insulin is to mimic as closely as possible the insulin profile of a person without diabetes; however, maintaining optimal blood glucose control remains the risk of hypoglycaemia. Today it remains the ultimate drug for reducing hyperglycaemia. Though it is regarded as the ultimate treatment for diabetes, side effects include hypoglycaemia, lipohypertrophy, hypersensitivity, atherogenic, metabolic, renal, gastrointestinal distress and so on [10].

1.3 Herbal therapy

Importance of natural products in DM treatment: Ayurveda and other Indian literature advocate the use of medicinal plants in the treatment of various human diseases. Phytotherapy has long been used effectively in treating diseases/disorders in Asian communities and throughout the world. Among 45,000 plant species in India, several thousands have been claimed to possess medicinal properties. The mechanism of action of most of the herbs and their bioactive derivatives used has not been scientifically

determined. Traditional antidiabetic plants might pave a way to new oral hypoglycaemic lead compounds, which can counter the high cost and poor availability of the current medicines/present day drugs for many rural populations particularly in developing countries. As they are considered to be free from toxic and side effects [11], the World Health Organization Expert Committee on diabetes recommended that traditional medicinal plants be further extensively investigated. The ethnobotanical information reports state that about 800 plants and their active extracts may possess antidiabetic potential [12]. Plants used in folk medicine to treat diabetes represent a viable alternative for the control of this disease.

Mechanism of action of anti-diabetic plants and their compounds: Research in the last few decades on plants demonstrated to have antidiabetic activity which is mentioned in ancient literature or used traditionally for diabetes are listed in Tables 1 and 2. The mechanism of action of medicinal plant compounds was represented in Fig. 3 [80]. Herbal formulations have reached widespread acceptability as therapeutic agents for diabetes. Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants. For instance, *Galega officinalis* was found to be rich in guanidine, a substance with blood glucose-lowering activity that formed the chemical basis of metformin [81]. This insulin sensitising drug was introduced in 1957.

Classification of anti-diabetic plants: The wide range of phytochemicals, which appear to be the active hypoglycaemic principles, suggests different sites of action within the body. Based on the possible mechanism of action, reported plant antidiabetics may be classified as follows.

a. *Insulin mimic herbs*: Presence of insulin-like substances/ proteins was reported in plant materials like onions, lettuce, green bean leaves and so on [82]. The purified protein extract of the fruits, seeds and callus of *Momordica charantia* (bitter gourd) which was reported to be homologous to animal insulin and Ginseng polypeptide, isolated from the root of *Panax ginseng* both showed significant hypoglycaemic activity demonstrated in vivo.
b. *β-cell stimulant herbs*: Leaf extract of *Azadirachta indica* significantly blocked the inhibitory effect of serotonin on insulin secretion mediated by glucose [83]. Oral administration of extract of Eugenia jambolana stimulated insulin secretion besides inhibiting insulinase activity from liver and kidney [84]. Brahmachari and Augusti [85] reported that the petroleum ether extract of dried onion has hypoglycaemic activity and can substitute tolbutamide in controlling alloxan diabetes in rats.
c. *β-cell regenerating herbs*: Epicatechin, isolated from the heart-wood of *Pterocarpus marsupium*, showed regeneration of the b-cell population of the islets, which were earlier necrosis by alloxan [86]. *Tinospora cardifolia* has insulin-like action and significantly reduced the blood glucose but not the lipid levels in alloxan-induced rabbits [87].
d. *Glyoxalase 1 activity enhancing herbs*: The powdered seed of *Trigonella foenum graecum*, in diabetic rats, reversed the activity of glyoxalase 1 to control values and re-stored the other general biochemical parameters [88].
e. *Glucagon inhibiting herbs*: Glucose levels in diabetic patients were decreased by *Ke-Tang-Ling*, an oriental antidiabetic drug with an inhibitory effect on glucagons secretion from a-cells in the pancreas [89].
f. *Glucose absorption reducing herbs*: Petroleum extract of *Cyamopsis tertragonoloba* showed a progressive decrease in the amount of HbA1c [90]. Alcoholic extract of alcoholic extract of leaves of *Ocimum sanctum Linn.* (Tulasi) reduced glycaemia in normoglycaemic, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats [75].
g. *Aldose reductase inhibiting herbs*: Roots and rhizomes of *Glycyrrhiza glabra* [91] and the bark of *Cinnamomum* cortex [92] inhibited rat lens aldose reductase activities.
h. *Glucose utility enhancing herbs*: *Cyamopsis tetragonolobus* (Gowar plant) [93] and *Grewia asiatica* (phalsa) [94] are reported to produce hypoglycaemia by modifying utilisation. Pectin from fruits of *Coccinia indica* also demonstrated hypoglycaemia probably due to decreased absorption of glucose from the intestine [95].
i. *Glycogen metabolic enzyme inhibiting herbs*: Trihydroxy octadecadiene acids from *Bryonia alba* were found to have an impact on glycogen phosphorylase, phosphoprotein phosphatase and hexokinase in the liver and muscle tissues of alloxan induced diabetic rats [96].
j. *Creatine kinase increasing herbs*: *Trigonella foenum graecum* normalised the decreased levels of creatine kinase in heart, skeletal muscle and liver of experimental diabetic rats and restored the normoglycaemia [97].

2 Need for nanotechnology

Phytotherapeutics needs a scientific approach to deliver the herbal drugs in a sustained manner to increase patient compliance and avoid repeated administration, which can be achieved by designing novel drug delivery system. Nanotechnology is one such approach that helps to increase the therapeutic value by reducing toxicity and increasing the bio-availability besides reducing repeated doses. It is a part of drug delivery systems where the drug is uniformly distributed in the body through the blood stream and is delivered at only specific sites thereby improving the therapeutic index. Nanostructured-based drug delivery system offers many advantages, some of which include: (i) they can pass through the smallest and narrow capillary vessels due to their ultra-tiny volume; (ii) they can penetrate cells and tissue gap to arrive at target organs such as liver, spleen, lungs, spinal cord and lymph [98]; (iii) they can provide controlled release for prolong period. These unique properties make nanostructured-based drug delivery system a better choice to deliver drug compared to conventional drug delivery system. The animal experiments demonstrated that the nanoparticles (NPs) enter the bloodstream and end up in organs such as liver and kidney. NPs also are able to protect the drug from degradation in the gastrointestinal tract, release the incorporated drug in a controlled manner thereby minimising side effects [99].

2.1 NPs in drug designing

Complementary and alternative drug formulations need to be developed using several existing phytochemicals already in traditional use to treat several symptoms of diabetes and its complications. However, orthodox medicines were proven to be superior to herbal drugs in the onset of action in spite of substantial amounts of phyto-antioxidants in herbs. The reason behind this is that their efficacy is seen only in long-term treatment and hence research is needed to enhance their action and bioavailability to targeted organs/organ systems. NPs and nanoscaled materials have many physical, chemical and biological properties that render them attractive for biomedical applications [100]. They are usually in the range of 100–1000 nm, however, some of the minute NPs, which are smaller than 100 nm across, attract water on the inside and are water repelling on the outside [101]. When they reach the bloodstream, they break down in response to the pH of blood and then release the drug. NPs are used to deliver both small-molecule and large macromolecular (i.e. DNA, RNA and proteins) therapeutics, as well as to diagnose and monitor the progression of disease [102]. Biosynthesis of NPs using plant extracts is the favourite method of green, exploited to a vast extent because the plants are widely distributed, easily available, advancement over physical and chemical methods, safe to handle and with a range of metabolites and compatibility for pharmaceutical and biomedical applications as they do not use toxic chemicals in the synthesis protocols [103–106]. The nanodrug proves to be an alternative approach for an optimised cost-effective use of the original drug substance as they enter the body in nanoform. In this way, nanodrugs are advantageous not only by their biodegradable, biocompatible and non-toxic nature, but also have greater ability to

Table 1 Plant proteins, alkaloids, aaponins and glycosides with antidiabetic activity

Plant name	Proteins, alkaloids, saponins and glycosides	Biological activities
Momordica charantia	p-insulin	hypoglycaemic [13]
Momordica cymbalaria	Mcy protein	antidiabetic [14], antihyperlipidaemic [15]
Acacia melanoxylon	protein	antidiabetic [16]
Dioscorea dumetorum	alkaloid dioscoretine, dihydro dioscorine	hypoglycaemic [17], antioxidant [18]
Equisetum myriochaetum	kaempferol glucosides, caffeoyl glucoside, kaempferol-3-osophoroside-4′-O-beta-D-glucoside	hypoglycaemic [19]
Ephedra distachya	ephedran C	anti-inflammatory [20], hypoglycaemic [21]
Ficus religiosa	β-sitosteryl-d-glucoside	anti-inflammatory [22], anti-diuretic [23], antidiabetic [24]
Vinca rosea	catharanthine, vincristine, vinblastine	anti-tumour [25], hypoglycaemic [26]
Withania somnifera	somniferine, somnine, withananine	hypoglycaemic [27], anti-tumour [28]
Xanthium strumarium	quinone, coumarin	anti-malarial [29] antidiabetic [30]
Stevia rebaudiana	stevioside	antimicrobial [31] and anti-inflammatory [32], antidiabetic [33]
Ipomea batatas	an acidic glycoprotein	antioxidant [34], antidiabetic [35]
Galega officinalis	alkaloid-galegine	anti-tumour [36], antidiabetic [37]
Kalanchoe pinnata	bryophyllin A	nephroprotective [38], antidiabetic [39]
Panax ginseng	ginsenosides	anticancer [40], anti-hyperglycaemic [41]

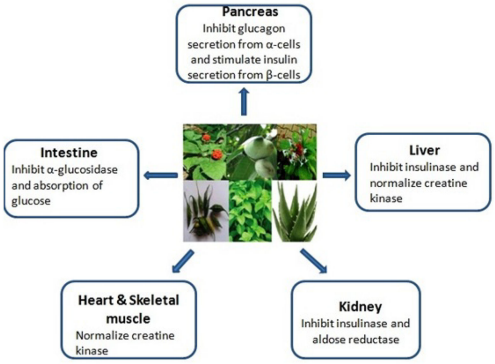

Fig. 3 *Mechanism of action of medicinal plants*

enter cells and so faster action [107]. The mechanism of action of nanodrugs is represented in Fig. 4.

2.2 Nanoforumulation of antidiabetic herbal drugs

Though many approaches for treating the disease have arisen throughout the years and new therapeutic targets are being identified, herbal therapy remains the mainstay of managing diabetes. Plants are an excellent source of secondary metabolites, and have been found to be cost-effective and eco-friendly for the large-scale synthesis of NPs [109]. In diabetic pigs, the pill

Table 2 Plant polyphenols and resins with antidiabetic activity

Plant name	Polyphenols and resins	Biological activities
Abelmoschus moschatus	myricetin (3,5,7-trihydroxy-2-(34,5 trihydroxyphenyl) chromen-4-one)	antidiabetic [42], antimicrobial and anti-proliferative [43]
Bauhinia variegata	flavonoids	antidiabetic [44], hepato protective [45], antimicrobial [46]
Murraya koenigi	quercetin, murrayacine, carbazole	antioxidant [47], hypoglycaemic [48], antifungal [49]
Quercus infectoria	quercetin	α-glucosidase [50], anti-proliferative [51]
Syzygium cumini	ellagic acid, isoquercetin, kaempferol, myrecetin	antioxidant [52], antidiabetic [53]
Tinospora cardifolia	tinosporide, tinocardioside	antidiabetic [54], immune modulatory [55]
Trigonella foenum graecum (Fenugreek)	kaempferol 3-O-β-D gluco pyranoside	antidiabetic [56], anti-apoptotic [57]
Abroma augustum	abromine, its hydrochloride and a phytosterol	antimicrobial, antidiabetic and hypolipidemic [58]
Bougainvillea spectabilis	D-pinitol (3-O-methyl-chiroinositol)	antidiabetic and hypolipidemic [59], antimicrobial and antiulcer [60]
Bacopa monnieri	hersaponin, bacoside A	antibacterial [61], antilipid peroxidative [62], hypoglycaemic [63]
Caesalpinia bonducella	caesalpin F	antidiabetic [64], anti-inflammatory [65]
Zingiber officinalis	isovanillin, 6-gingerol, 6-shogaol	antidiabetic [66], neuro-protective [67]
Cystoseira barbata	polypeptide	hypoglycaemic [68]
Pterocarpus marsupium	pterocarpol, pterostilbene	antihyperglycaemic [69], antimicrobial [70]
Rhizophora apiculata	thymoquinone, carvacrol	hypoglycaemic [71], antioxidant [72]
Nigella sativa	thymoquinone, thymol	hypoglycaemic [73], anti-inflammatory [74]
Ocimum sanctum	eugenol	antidiabetic [75], antihypertensive [76]
Ginkgo biloba	ginkgo-flavone glycosides fraction-quercetin, kaempferol	antimicrobial [77], antidiabetic [78], antioxidant [79]

containing the NPs led to control of blood glucose after eating [110]. By considering the nanosuspension formulation for medicinal plants or their phyto-compounds, it may improve the poor water solubility of medicinal plants or their phyto-compounds and can be used for investigation of biological activity [111]. On the ultimate way to pharmacy, nanoformulations need to be characterised before preclinical and clinical studies. Thus, the nanoformulation exhibited significantly enhanced anti-diabetic activity compared to marketed products.

Non-metals: Lipid-based nanoemulsion of phytochemicals from *Tinospora Cordifolia* improved their oral antidiabetic efficacy [112] and encapsulation of *Phaleria macrocarpa* leaf extract demonstrated to possess potent antihyperglycaemic activity [113]. PLGA nanoencapsulated forms of *Syzygium jambolanum* [114] and *Gymnema sylvestre* [115] have been tested and shown to have relatively more anti-hyperglycaemic effects than their un-

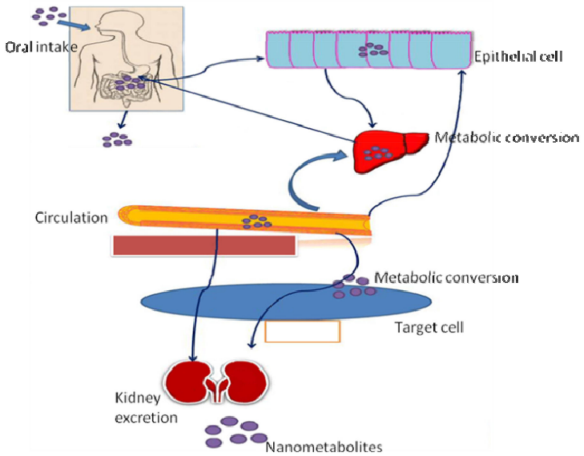

Fig. 4 *Mechanism of action of nanodrugs*
Courtesy: Palanivel Ganesan *et al.* 2017 [108]

Table 3 NP encapsulated herbal drugs

NP type	Plant	Plant source used
non-metals		
lipid based	*Tinospora Cordifolia*	phytochemicals
	Phaleria macrocarpa	leaves
	Talinum portulacifolium (Forssk.)	flavonoids and tannins
PLGA	*Syzygium jambolanum*	phytochemicals
	Gymnema sylvestre	gymnemic acids
AgNPs	*Costus pictus*	leaves
	Sphaeranthus amaranthoides	extract
AuNPs	*Mirabilis jalapa*	flowers
	Cassia fistula	stem bark
	Gymnema sylvestre	leaves
Au–Ag NPs	*Cinnamom camphora*	leaves
	Ocimum basilicum	leaves and flowers
CuNPs	*Dioscorea bulbifera*	extract

encapsulated counterparts in various experimental models dominating a wide range of therapies in treating diabetes. The lipid-based nanoformulation of the ethanolic extract of *Talinum portulacifolium* (Forssk.) at the dose of 250 mg/kg body weight produced significant antidiabetic activity in streptozotocin and high-fat diet-induced diabetic rats. The activity was attributed due to the presence of flavonoids and tannins in the extract [116].

Silver NPs (AgNPs): Green synthesis of *Costus pictus* leaves AgNPs are found to be exceptionally stable, and also minimise toxicity and cost. It may be better therapy for treating diabetes instead of other formulations [117]. Swarnalatha *et al.* [118] explored the *Sphaeranthus amaranthoides* biosynthesised AgNPs by inhibiting α-amylase and acarbose sugar in diabetes-induced animal model. It is mainly due to α-amylase inhibitory components present in the ethanolic extract of *S. Amaranthoides*.

Gold NPs (AuNPs): Several medicinal plants and extracts have been used for the biological synthesis of AuNPs [119]. The synthesis of AuNPs from the extract of the *Mirabilis jalapa* flower [120] showed the formation of AuNPs with a characteristic size of 100 nm and spherical in shape. Streptozotocin-induced diabetic rats, on treatment with nanoform using the stem bark of *Cassia fistula* significantly induced favourable changes in body weight, reduced serum blood glucose concentrations, improved the lipid profile and transaminase activity and also reversed renal dysfunction far better than the aqueous extracts alone [121]. The antidiabetic activity of AuNPs synthesised using the antidiabetic potent plant Gymnema sylvestre R. Br on wistar albino rats has been evaluated [122].

Au–Ag NPs: Sun-dried *Cinnamom camphora* leaf was also evaluated through the synthesis of nanosized noble metals of gold and silver by Huang *et al.* under ambient conditions [123]. NPs were also synthesised from the leaves and flowers of *Ocimum basilicum* [124].

Copper NPs (*CuNPs):* CuNPs using *Dioscorea bulbifera* extract were found to possess antidiabetic and antioxidant activities [125]. It was also the first time to demonstrate the potentiality of CuNPs as antidiabetic agents due to their inhibiting activity on both porcine pancreatic α-amylase as well as crude murine pancreatic and intestinal amylase. It also provides considerable evidence on the antidiabetic promises of biogenic CuNPs, as potential preventive agents towards the initiation and development of free radical-induced DM and its complications [126].

Nanoformulation of stevioside from the leaves of *Stevia rebaudiana* is expected to behave as a better antidiabetic drug with increased bioavailability too than the drug alone [127]. *Momordica charantia* consisting antidiabetic principles has been nanoformulated which significantly inhibited α-glucosidase and α-amylase enzymes in vitro [128]. Fasting blood glucose in T2DM rats treated with encapsulated Chinese propolis (a herbal resinous substance obtained from buds of many medicinal plants) was significantly reduced compared with diabetic controls [129]. The results also show that encapsulated propolis inhibited the increased levels of triglycerides in T2DM rats, probably by its action on insulin sensitivity and lipoprotein lipase activity in treated diabetic rats. Merrell *et al.* [130] evaluated antidiabetic, antioxidant and wound healing activities of nanoencapsulated Curcumin in male C57/B6 mice at different concentrations. Propanoic acid, a bioactive component from *Cassia auriculata* was encapsulated by AuNPs and the antidiabetic potential of the formulation was assessed by Venkatachalam *et al.* [131]. The blood glucose, triglycerides and cholesterol levels were decreased in the diabetic treated rats besides improved insulin levels at a concentration of 0.5 mg/kg body weight. A brief review of nanoencapsulation of herbal compounds is listed in Table 3.

Toxicity studies of NPs: Lockman *et al.* [132] suggested that the surface charges of NPs should be considered for toxicity and brain distribution profiles further investigating that neutral and anionic NPs at low concentrations had no effect on blood–brain barrier integrity, whereas, higher levels of anionic and cationic NPs were proved to be toxic. However, cationic NPs lead to blood clotting and haemolysis while anionic NPs were non-toxic [133]. A recent review of Costigan [134] reported the toxicity of NPs in healthcare products and concluded that the toxicity data of NPs in use was very limited and further scientific investigations are required to reveal the chronic toxic effects of NPs.

3 Future prospective

Nanotechnology, nowadays has given new hope for the formulation of various drugs against many dreadful diseases, including diabetes. Nanotechnology in the past three decades has brought significant innovations to the pharmacology [135]. Engineered nanomaterials, one of the nanotechnology applications, have already become part of human daily life as food packaging agents, drug delivery systems, therapeutics, biosensors and many more. Targeted drug delivery is intended to reduce the side effects of drugs with concomitant decreases in consumption and treatment expenses. Drug delivery focuses on maximising bioavailability both at specific places in the body and over a period of time. This can potentially be achieved by molecular targeting by nanoengineered devices [136]. The nanodevices are faster and more sensitive than typical drug delivery [137]. The efficacy of drug delivery through nanomedicine is largely based on: (i) efficient encapsulation of the drugs, (ii) successful delivery of drug to the targeted region of the body and (iii) successful release of the drug. Formulation of nanodrugs based on their molecular mechanism of action is the basis of nanotechnological approaches involved in several studies. The efficacy of NPs to modulate several biomarkers depending on their amount taken for encapsulation and the final yield after nanoformulation proves the potentiality. Damge *et al.* [138] explored the potential of NPs-encapsulated insulin to improve the oral bioavailability of insulin. They observed that insulin NPs decreased fasted glycaemia in a

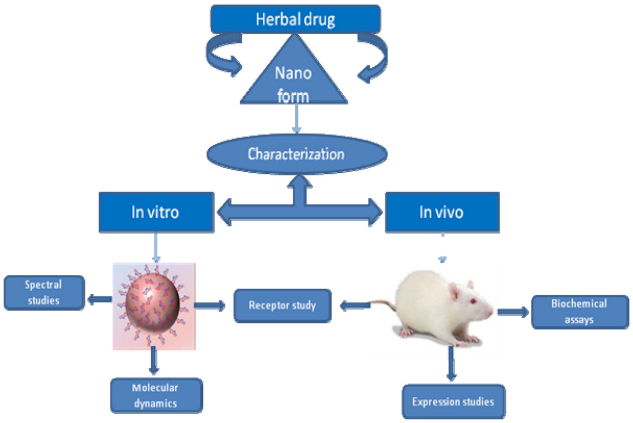

Fig. 5 *Schematic representation of herbal nanomedicine and its therapeutic evaluation*

 – nanoherbal drug,  – diabetic rat. Characterisation studies of nanodrug followed by in vivo actions leading to ideal formulation of a herbal drug

dose-dependent manner in diabetic rats and also showed that insulin NPs increased serum insulin levels and improved the glycaemic response to an oral glucose challenge for a prolonged period of time (Fig. 5).

In the present review, different plant/plant parts or their active principles have been nanosynthesised for treatment of type 2 diabetes. 'Herbal remedy' in the nanocarriers will increase its potential for the treatment of various chronic diseases and health benefits. Nanotechnology is being used to improve the ease, efficacy and safety of insulin replacement therapy [139, 140]. Newer approaches of modern drug delivery system, i.e. 'Nanotechnology' have established the attractive therapies to the pharmaceutical in the near future that will enhance the health of people. With the increasing population of diabetics, improved resources are needed to sustain society and this could be achieved through nanoscience and technology. With this new technology, diabetics may become completely free from dietary regulations and the restrictive systematic regime.

4 Conclusion

Herbal medicine is the oldest form of healthcare known to mankind. It is an integral part of the development of modern evaluation. Nanotechnology is well accepted in improving the performance and dosage of drugs and also enhances the drug efficacy. It increases the effectiveness, safety as well reducing the ultimate healthcare costs. The size of nanomaterial is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications and drug delivery vehicles. Hence, nanotechnology is promising to serve as a good choice of drug delivery system for the more challenging conventional drugs used for the treatment and management of chronic disease like diabetes. At the same time of application, method of application and doses of application play an important role to signify the toxic effects of nanoscale drugs which cannot be ignored.

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