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Research article

# Holistic care management for diabetes mellitus: A futuristic approach

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## ABSTRACT

The public health concern is very important for the growing burden of chronic metabolic disease like Diabetes mellitus. It is foreseeable that by 2045 India would reach rank first in Type-2 Diabetes Mellitus which contributes to 90% of diabetes. Therefore, more care or attention should be given to this disease. There are so many medications available in the market including herbal drugs. But due to more side effects of oral hypoglycemic agents, attention grabs more towards the alternative of synthetic drugs or using Nano-carriers to avoid side effects. Presently, many novel drug delivery systems for oral hypoglycemic agents are available in the market. But herbal drugs grab more attention due to lesser side effects, efficacy and cost-effective. However, there is very less work is reported on nanotechnology like liposomes, nanoparticles/microparticles, gold nanoparticles, noisome, and nano-capsules/microcapsules of herbal drugs, which is currently emerging therapy for diabetes. Nanotechnology or a novel drug delivery system for herbal medicine can be used to overcome the challenges like poor bioavailability, efficacy and stability problems. The current review emphasizes current epidemiology, its types, complications and management of different treatment strategies for diabetes mellitus. Furthermore, the problems related to herbal medicine with immense hope for herbal medicine using nanotechnology are discussed.

**Keywords:** DM, T1DM, T2DM, gestational diabetes, herbal medication, nanotechnology, novel drug delivery system

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## INTRODUCTION

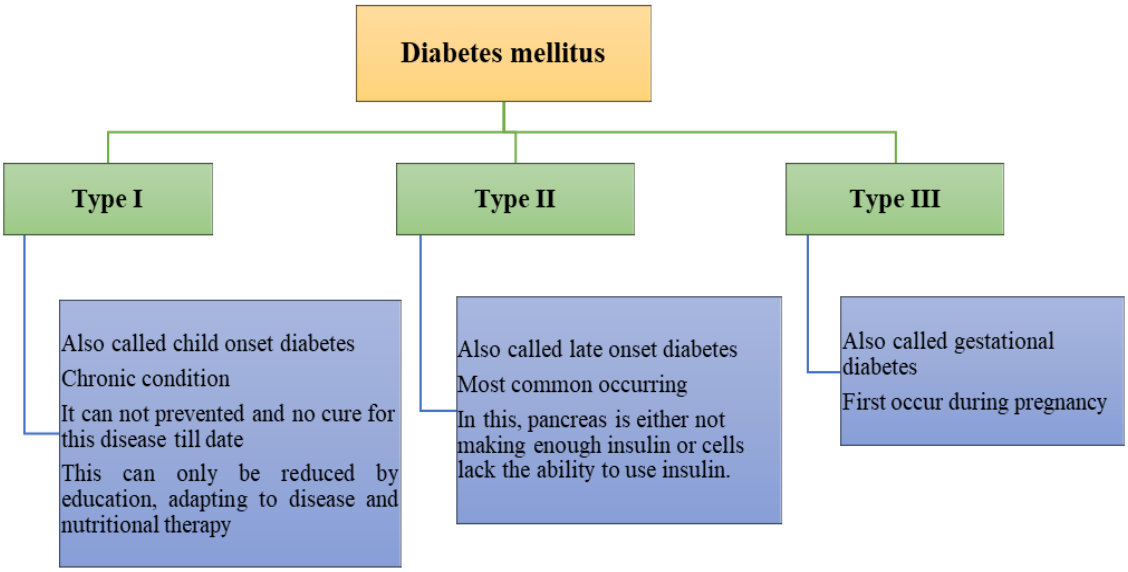
Diabetes mellitus is a long-term metabolic condition associated with high hyperglycaemia, glycosuria, and a negative nitrogen balance. Thickening of capillary endothelium, enlarged vessel wall matrix, and cellular proliferation are common pathological modifications that contribute to vascular problems such as lumen shrinkage, early coronary plaque, retinopathy, neuropathy, and peripheral vascular inadequacy.

Nowadays, China among all countries got the first rank with this life-threatening disease due to a greater number of people of young age up to elderly age, and this trend is followed by India and America. It is foreseeable that in 2045 India will reach rank 1st, then America [1]. T2DM contributes to 90% of diabetes, other factors like aging, diet culture, and urbanization may increase the intensity of this disease. T1DM is also increasing the incidence rates, contributing to more diabetic cases [2]. There are so many other undiagnosed cases in developing countries due to a lack of education about the disease. In women, there are the chances of occurrence of Gestational DM from the 4th month up to the last month of pregnancy which intensify the future risk of T2DM with the incidence of 35–60% or sevenfold soon after delivery compared with normal glycemic pregnancy [3,4]. The prevalence of disease in India was assessed by territory, rural vs urban place, sexual category, and age group. Results showed the prevalence of disease according to sex and age was 7.3% in women and 7.8% in men with which 2.4% in younger ages and 14% in older ages. As per location, Diabetes was more frequent in South India (Andhra Pradesh, Goa, Karnataka, Kerala, and Tamil Nadu) as well as in Delhi from north India and West Bengal from east India [5].

Depending upon the contexts existing at the time of diagnosis, Diabetic patients are difficult to categorize into a single group when it comes to assigning a type of diabetes. Generally, diabetes is classified into 3 main types as per described in figure 1. 1) Type 1 Diabetes Mellitus (due to autoimmune β-cell destruction, typically foremost to complete insulin scarcity), 2) Type 2 Diabetes Mellitus (insulin resistance), and 3) Gestational diabetes (diagnosed in the second or third trimester of pregnancy). There are so many other reasons to induce diabetes like an inherited deficiency in β-cell functions, inherited failure of insulin action, defect of the exocrine pancreas, certain drugs that cause diabetes i.e. diazoxide, thiazides, glucocorticoids, thyroid hormones, and many more, and certain infections like congenital rubella, cytomegalovirus and others [6,7]. The disparity between T1DM, T2DM, T3DM, and other forms of

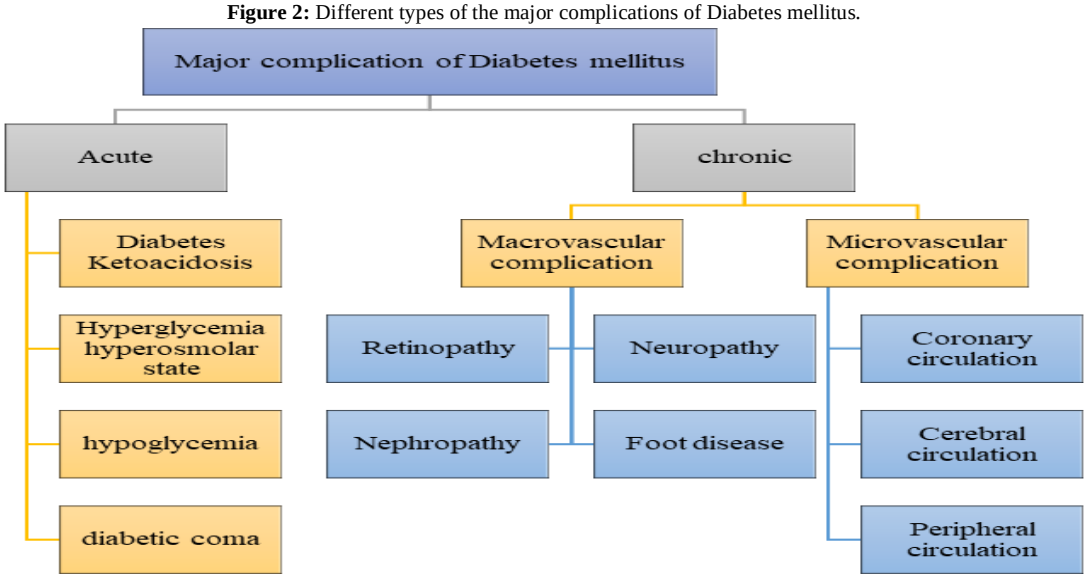
diabetes has significant associations for both treatment and education [8]. Children of diabetic mothers were at greater threat of attention deficit/hyperactivity disorder [9]. The exact cause for T1DM is yet unspecified; Scientists believed that there is inherent susceptibility strongly connected with human leucocyte antigen. Malnutrition-related diabetes mellitus (MRDM) describes the state of juvenile diabetics in tropical emerging economies who have a background of malnourishment and a group of signs that do not fit the T1DM and T2DM criteria [10]. Subclasses of MRDM are; i) Fibro calculous pancreatic diabetes (FCPD) caused due to consumption of food containing cyanogenic glycosides such as cassava [11], and ii) Protein deficient pancreatic diabetes (PDPD) that occurs due to childhood malnutrition that leads to β cell damage [12].

**Figure 1:** General classification of Diabetes Mellitus.




The occurrence of this disease has been widespread all over the world. Diabetes depends on its duration and severity and affects nearly every organ system in the body. Although long-lasting diabetes has very common gastrointestinal (GI) complications like abdominal pain, nausea, vomiting, and abnormalities in liver function tests but have very low awareness among doctors. Hepatic dysfunction is caused due to NAFLD(nonalcoholic fatty liver disease) in T2DM, and liver dysfunction in T1DM usually results from glycogenic hepatopathy [13]. Different grades of Ketoacidosis progressively occur in T1DM. It is very uncommon in T2DM. This abnormal accumulation of glucose ultimately leads to very life-threatening complications which can be acute or chronic in type (microvascular or macrovascular complications). This includes diseases of the Heart, kidneys, eyes, and more [14]. Diabetes is also linked with changes in plasma lipid and lipoprotein profiles that will lead to an augmented risk of coronary heart disease.

**Figure 2:** Different types of the major complications of Diabetes mellitus.



Hyperlipidaemia has been graded as one of the greatest threats to cause atherosclerosis, stroke, and coronary heart diseases [15]. In another experiment, an animal model was first induced into the disease by different agents like Zinc Chelators, Alloxan, Streptozotocin (STZ), and viruses and then used animal models for the study and treatment of micro and macrovascular complications of DM. DM-induced hyperglycaemia causes the binding of the AGEs(Advanced glycation end products) with its receptor RAGE, which induced infiltration of inflammatory cells with reactive oxygen intermediates resulting reduction of NO and inhibiting the synthesis of prostacyclin. This results in the damage of the properties of the endothelium like antithrombotic and vasodilating, that causes the progression of the disease [16].

**Data collection**

The data for this study were retrieved from Scopus, Web of Science, PubMed, and Google Scholar. Web of Science and Scopus was chosen as search engine because it is the most widely accepted and frequently used database for the analysis of scientific publications.

**Recent advances in anti-diabetic drugs**

The important elements to treat diabetes are Diet (with exercise if possible)**.** Diabetics should focus on • Weight control • Nutritious diet that allows blood glucose levels as near to normal as possible • Check on blood lipid profile • Oral hypoglycemic agents [17].

Oral hypoglycemic agents are present in the market to treat T2DM but one or more associated side effects like weight gain, hypoglycemic shock, etc. lead to more concern about the treatment. New drugs with effective treatment with the least side effects are still investigating. Here is the need required to make a novel drug delivery system for the treatment. There are so many Oral hypoglycemic agents with novel drug delivery systems available in the market and some under clinical trials. Here are the lists of Oral hypoglycemic agents with the example of novel drug delivery systems.

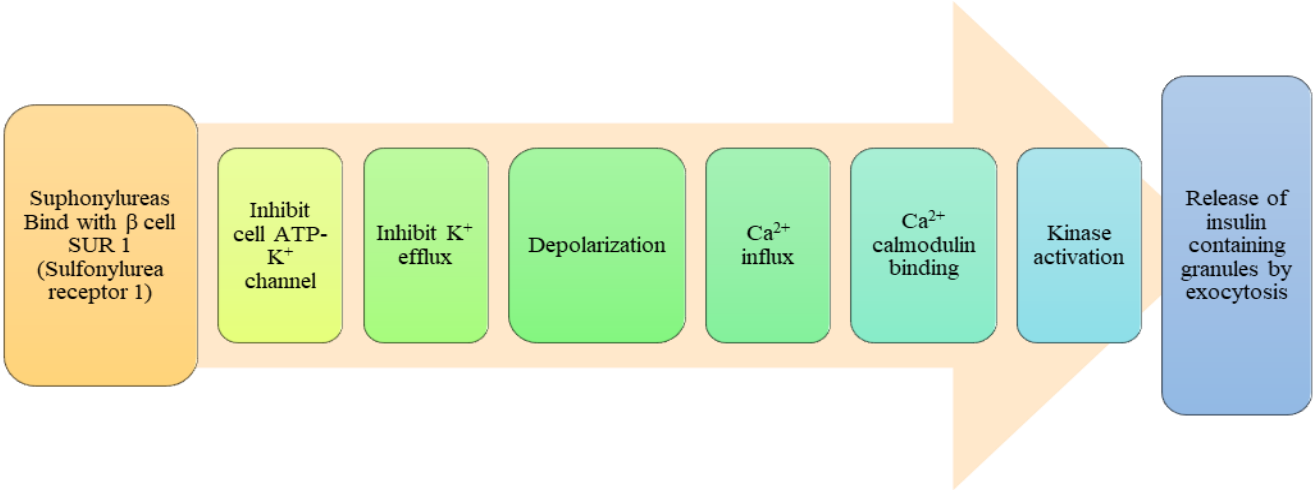
**Biguanides**

Biguanides are classified on the presence of a bio guanidine molecule. These molecules initially were derived from the plant Galega officinalis [18]. Biguanides enter into hepatocytes via OCT1 (Organic cation transporter 1) which leads to drug accumulation in the cell. Moreover, the accumulative drug inhibits mitochondrial complex 1, inhibits the production of ATP (Adenosine triphosphate) leads to an increase in the cytoplasmic ratio of ADP: ATP (Adenosine diphosphate: Adenosine triphosphate) & AMP: ATP (Adenosine mono-phosphate: Adenosine triphosphate. Activation of AMPK (5' AMP-activated protein kinase) causes inhibition of gluconeogenesis and stimulation of the fatty oxidation that increases insulin sensitivity [19]. But Phenformin and buformin also showed severe side effects like acidosis was taken off in the 1970s [20]. A potential diabetes analysis was conducted in the UK in the late 1970s (UKPDS) for metformin. Furthermore, metformin was shown for the first time to lower blood glucose and protect cardiovascular function, particularly in obese patients. It was approved by US FDA in 1994 for type 2 DM [21]. At present date, there are so many formulations present in the market either single or combined forms. Sustained Release floating tablets of metformin help to control and sustainable release with better bioavailability [22].

**Sulphonylureas**

The primary effect of sulfonylureas is an increase in plasma insulin levels. This happens in two ways either by stimulation of insulin secretion by β cells of the pancreas or reduction of hepatic clearance of insulin [23].

**Figure 3:** Mechanism of Action of Sulphonylureas




The mechanism of action of this generation is well explained in figure 3. In most cases, sulfonylureas are well accepted. But Hypoglycemia is the most known side effect, which is especially prevalent with long-acting sulfonylureas like chlorpropamide and glibenclamide [24]. Glimepiride was linked to fewer instances of severe hypoglycemia in patients with type 2

diabetes than glibenclamide in clinical trials. Glimepiride did, however, cause severe hypoglycemia, which might be avoided if treatment targets are defined on an individual basis [25]. To overcome these side effects due to overloading of drugs or toxicity, there are so many formulations like microemulsions for control release [26], fast-dissolving tablets to improve bioavailability [27], microspheres [28], fast-dissolving oral films for easily dissolved in the buccal cavity [29], liposomes increase bioavailability [30], microemulsion claimed to improved clinical efficacy [31], self-emulsifying delivery system (SEDDS) helps to improve its dissolution properties [32] and many more are already exist.

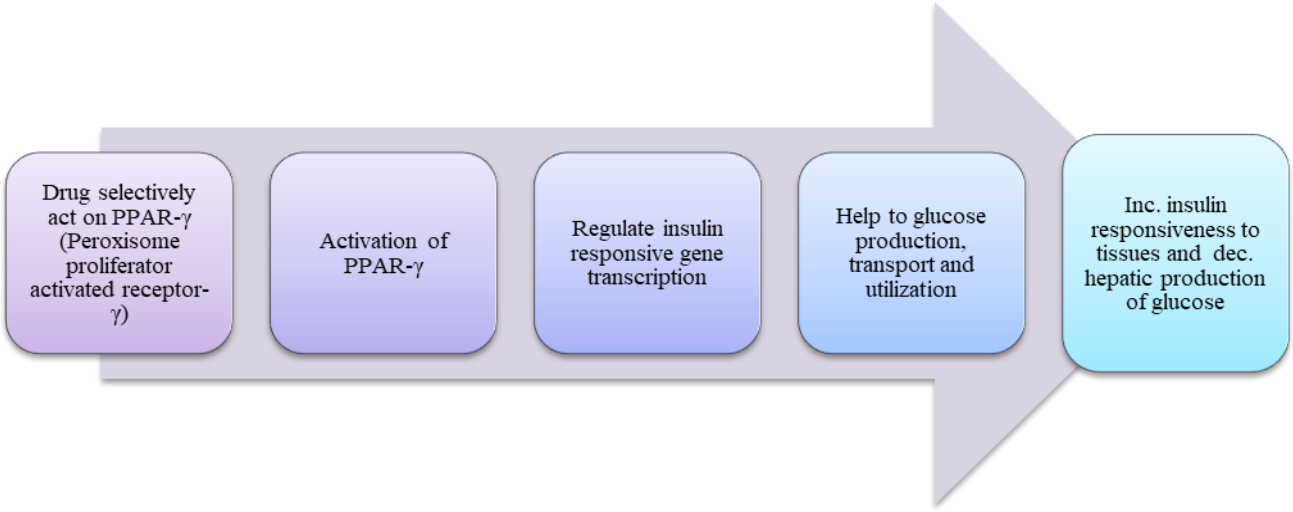
**Meglitinide**

Postprandial glycemia is neither targeted nor adequately controlled by conventional oral hypoglycemic medications. For the first time, new classes of oral agents with a more precise mode of action have emerged, allowing for the restoration of early-phase insulin release. Meglitinide analogues are one such pharmacological class (repaglinide, Nate glinide, and Miti glinide). These medications are ideal for usage in conjunction with metformin[33]. Extracellular glucose has a stimulatory influence on the ATP-sensitive K+ channel. As a result, it is more successful in lowering post-prandial glucose levels than it is at lowering fasting glucose levels. Meglitinides may be used as a substitute for metformin in cases when the side effects of metformin are unacceptable (persistent diarrhea) or if metformin is unsuitable [34].

**Thiazolidinediones**

The only pharmacologic medicines that directly treat insulin resistance are thiazolidinediones (TZDs). The well-understood mechanism is explained in figure 4. The conventional dosage form of Rosiglitazone is a well-tolerated drug but Increases the risk of fractures, especially in elderly women, CHF may be precipitated and contra-indicated in liver disease. According to the latest findings, rosiglitazone-related cardiovascular toxicity and pioglitazone-related increased risk of bladder cancer are no longer serious concerns [35]. Microcapsules of Rosiglitazone showed the released drug in a more controlled manner [36]. Obesity was treated by injecting NPs into white adipocytes, which caused local browning activity without causing any side effects [37]. The adhesive transdermal patches of Pioglitazone avoid first-pass metabolism, but in vivo studies on humans still need to be carried out [38]. Lipid-based Pioglitazone nanoparticles showed higher hypoglycemic activity than pure Pioglitazone dispersion [39].

**Figure 4:** Mechanism of Action of Thiazolidinediones




**Alpha-glucosidase inhibitors**

long chain polysaccharides are broken down into simple absorbable monosaccharide units by carbohydrate-digesting enzymes located in the brush border of the intestine. α-Glucosidases are the enzymes that help to absorb monosaccharides or glucose by disrupting the -glucopyranoside linkage in oligosaccharides or disaccharides and regulating glucose availability and the extent of hyperglycaemia after eating [40]. As the name suggested, Alpha-glucosidase inhibitors reversibly inhibit α- glucosidases, with no clinically significant effects on lipid profile or body weight [41]. Conventional dosage forms of Acarbose and Miglitol are used as an adjuvant to diet in an obese patient, drug solubility in water is higher, and the half-life is short (2 h). For better patient compliance, reduce multiple doses and improved efficacy sustained-release microspheres were successfully formulated [42,43]. Voglibose is also another type of alpha-glucosidase inhibitor which is very less soluble in water and ethanol. It is poorly absorbed in the stomach like acarbose and is not FDA-approved [44].

**Incretin Agonist**

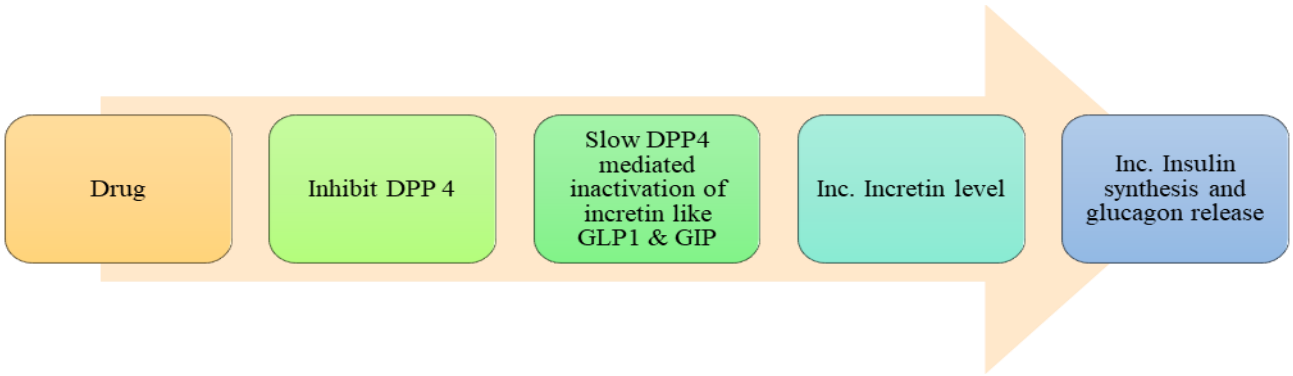
Incretin hormones are a type of peptide generated in the intestines that induce insulin release in the incidence of hyperglycaemia. GIP a type of incretin hormone, 42-amino-acid protein (glucose-dependent insulinotropic polypeptide), and GLP-1 (glucagon-like peptide-1) are formed in the upper K cell (GIP) and lower L cell (GLP-1,) of the stomach, respectively. They stimulate the release of insulin from pancreatic cells at high glucose levels.

This incretin impact is diminished or absent in persons who suffer from type 2 diabetes [45,46]. (GLP-1), Glucagon-like peptide-1 is a synthetic peptide therapeutic with structural and functional resemblance to the human incretin hormone. It also has significant body weight reduction [47]. Self-emulsifying drug delivery system (SEDDS) of Exenatide, an incretin agonist, has good relative bioavailability and is an assured tool for oral peptide delivery [48]. Liraglutide nano-capsules have a half-life of up to 13hr due to a decrease in the extent of metabolism [49]. So it is used as a promising vehicle, to deliver medicine to the gastrointestinal tract [50]. Nanoparticles showed no other accumulation of the drug in any major organ and the drug easily cleared out from the liver within 12 hours [51].

**DPP-4 Inhibitors**

DPP-4 is found in a variety of organs and circulation. DPP-4's major function is to break from the second amino acid of the N-terminal end with selectivity for alanine (as seen in GLP-1) or proline as the 2nd amino acid. As DPP-4 is very active so degrading the incretin hormones in circulation within minutes, so approach to inhibit the DDP-4 is useful to enhance the half-life and effects of incretin hormones [52]. The mechanism of action is fully described in figure 5. Metabolism of sitagliptin, a DPP-4 inhibitor**,** majorly mediated by cytochrome P450 3A4/5 and half time is 2.5 hrs. To overcome these limitations, many novel formulations like mucoadhesive formulations have prolonged the drug release time [53], Oral polymeric nano scaffolds for Control drug release [54], and Nanoparticles claimed to improve therapeutic efficacy in oral delivery [55] already exist in the literature. Furthermore, nanoparticles and nano-sphere are also claimed to enhance oral bioavailability [56] and effective oral delivery [57]. Transdermal patches of Sax gliptin have effective drug release [58]. Recent studies suggested that when GLP-1 receptor agonists are administered, DPP-4 inhibitors treatment should be avoided. As Oral antidiabetic drugs, DPP-4 inhibitors are used as a second-line therapy following metformin failure as insulinotropic drugs with no risk of hypoglycemia and no effect on body weight. Metformin fixed-dose formulations are commonly used [59].

**Figure 5:** Mechanism of action of DPP-4 Inhibitors




**SGLT2 inhibitors**

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are glucose-reducing medications that cause glucosuria by blocking glucose and sodium reabsorption in the kidneys [60]. SGLT2 is mostly found in the very first segment of the proximal tubule region of the kidney, where it is accountable for approximately 90% of glucose reabsorption at the glomerulus level [61]. In the context of a multidisciplinary approach, canagliflozin, together with other anti-hyperglycemic medicines has demonstrated positive cardiovascular effects and represents a unique prospect to improve glycemic control while lowering the risk of CV events in patients with T2DM [62]. Because urine glucose excretion reduces as blood glucose levels fall, SGLT-2 inhibition poses little danger of hypoglycemia [63]. In comparison to other drugs in the same category, such as tofogliflozin, dapagliflozin, and empagliflozin, canagliflozin has a lower selectivity for the SGLT-2 receptor over the SGLT-1 receptor [64]. Canagliflozin belongs to the BCS class 4 drug and has poor solubility and poor permeability; solid SMEDDS were successfully formulated and used as an alternate promising formulation [65]. There is immense hope to develop a novel drug delivery system of conventional oral hypoglycemic agents to increase efficacy, and safety and lessen the intensity of side effects. But still, there is lacking clinical trials or in-vivo data to evaluate the efficacy and side effects of oral hypoglycemic agents. This leads to going on with new approaches like using herbal medicine to treat DM which has lesser amount of side effects as compared to oral hypoglycemic agents.

**Future Perspectives of Herbal Drugs with Antidiabetic Potential**

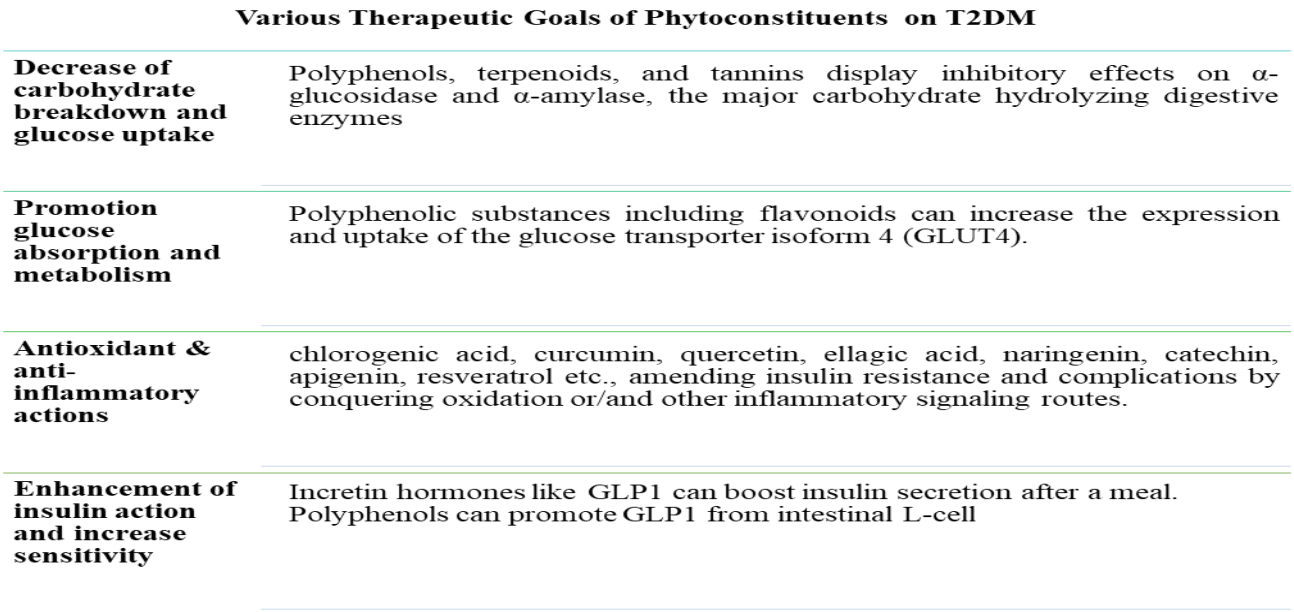
Although there have been numerous attempts to treat this disease over the years, and new therapeutic targets are being identified but herbal therapy persists as the backbone of coping with diabetes. Since ancient times, Ayurveda treated various human diseases with the use of herbal plants. The value of herbal medicine was recognized in 2015 when You you Tu was awarded the Nobel Prize in Physiology or Medicine for finding the antimalarial component artemisinin from Artemisia annua L. (Qinghao) [66]. Also, synthetic drugs have more side effects and are highly costly, so herbal plants as an alternative used to treat diabetes which can overcome the problems regarding the high cost, side

effects, and poor availability in developing countries [67]. F.J. Alarcon-Aguilara *et al* studied 28 antidiabetic plants and out of them, 8 show significant results. WHO Expert Committee also suggested further study for more accurate results [68]**.** Esmaeel Ebrahimi *et al* studied that secondary metabolites of plants like phenols, alkaloids, and flavonoids have significant effects on the treatment of complications of diabetes [69]. It is also claimed that treatment with herbal medicine lowered reactive oxygen species, improved cognition, and corrected T2DM-induced cognitive deficits [70]. Furthermore, plant components should be separated and their individual effects on diabetes mellitus examined. To date, there are so many herbal plants have been identified to treat Diabetes mellitus or its related complications to slow down its worsening effect but still, there is lacking *in-vivo* data on most of the herbal drugs. The only problem with herbal drugs is that there are no data on reported cases of the use of alternative 'herbal' medications alone in the treatment of T2DM 2 [71]. Moreover, 'herbal' medications are more adulterated with those components that were already withdrawn from the market due to serious adverse events [72]. So before going with herbal medication it should be purified, stabilized, evaluated, and properly labelled as allopathic drugs do. Xin Nie *et al* well explained multi-therapeutic targets of phytoconstituents on T2DM [73] as shown in figure 6. The novel preparations are intended to yield numerous advantages over existing formulations of plant actives or extracts, including better bioavailability, solubility, toxicity protective measures, pharmacological activity, stability enhancement, better cellular macrophage allocation, sustained delivery, and prevention from physical or chemical degradation [74,75]. Combination therapies of herbal plants are proven to be more effective. Farghaly *et al* formulated pharmaceutical capsules containing garlic, onion, and fenugreek seed powders in a 1:1:2 ratio that resulted in effective treatment against diabetes [76]. This area is still growing as many novel drug delivery systems can be used for herbal medication. The following table showed different types of delivery systems that can be used to prepare herbal medication.

**Table 1:** Different types of novel drug delivery system

| Novel Drug Delivery System | Size range |
|---|---|
| Liposome | 30 nm to several micrometers |
| Niosome | SUV-10–100 nm<br>MLV greater than 5 µm |
| Nano-/microcapsule | 10 nm to 1000 nm |
| Nano-/microparticle | 0.001 µm (1 nm) - 0.1 µm |
| Nanogel | 20-200 nm |
| Nanofiber | 500 nm to 50 nm |
| Enteric-coated tablets | -- |
| Trans-dermal system | --- |
| Mesoporous material | --- |

**Figure 6:** Various Therapeutic Goals of Phyto-constituents on T2DM




## CONCLUSION

There are so many medications either synthetic drugs or herbal medication available for the treatment of metabolic disease i.e. diabetes mellitus. Firstly, insulin and biguanides were discovered as effective treatments but biguanides were under the shade of the popularity of insulin. But after decades it was the most popular drug to treat disease. With time, there were discoveries of more new drugs like Sulphonylureas, Meglitinide, Thiazolidinediones, Alpha-glucosidase inhibitors, Incretin Agonists, DPP-4 Inhibitors, etc. They all are somewhat effective to treat disease but the cost and side effects associated with drugs lead researchers to explore the area of traditional herbal medicine with the least or no side effects and low cost. Novel drug delivery concepts also came into existence which leads to the making of many novel formulations of synthetic as well as herbal medicine. There are novel drug delivery systems for

synthetic drugs available in the market. But there is very little research work done on herbal medication collaborated with novel drug delivery systems. By using nanotechnology to formulate drugs it might be very helpful to treat disease with proper management, fewer side effects, and improve efficacy and safety, and stability. This novel drug delivery system would help to increase the stability of herbal drugs and increase bioavailability. Novel drug delivery system has been acknowledged for their definite profits, the significant capacity of offering stability, sustained or extended release, and site-specific drug action in the treatment of DM [77]. Thus, a novel drug delivery system using nanotechnology is a promising choice for the therapy of chronic diseases like DM. Furthermore, the toxic effects of herbal medication should also be considered and cannot avoid.

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