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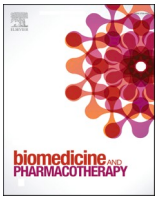

Review

Diabetes mellitus and diabetic foot ulcer: Etiology, biochemical and molecular based treatment strategies *via* gene and nanotherapy

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ABSTRACT

Diabetes mellitus (DM) is a collection of metabolic and pathophysiological disorders manifested with high glucose levels in the blood due to the inability of β-pancreatic cells to secrete an adequate amount of insulin or insensitivity of insulin towards receptor to oxidize blood glucose. Nevertheless, the preceding definition is only applicable to people who do not have inherited or metabolic disorders. Suppose a person who has been diagnosed with Type 1 or Type 2DM sustains an injury and the treatment of the damage is complicated and prolonged. In that case, the injury is referred to as a diabetic foot ulcer (DFU). In the presence of many proliferating macrophages in the injury site for an extended period causes the damage to worsen and become a diabetic wound. In this review, the scientific information and therapeutic management of DM/DFU with nanomedicine, and other related data were collected (Web of Science and PubMed) from January 2000 to January 2022. Most of the articles revealed that standard drugs are usually prescribed along with hypoglycaemic medications. Conversely, such drugs stabilize the glucose transporters and homeostasis for a limited period, resulting in side effects such as kidney damage/failure, absorption/gastrointestinal problems, and hypoglycemic issues. In this paper, we review the current basic and clinical evidence about the potential of medicinal plants, gene therapy, chemical/green synthesized nanoparticles to improving the metabolic profile, and facilitating the DM and DFU associated complications. Preclinical studies also reported lower plasma glucose with molecular targets in DM and DFU. Research is underway to explore chemical/green synthesized nanoparticle-based medications to avoid such side effects. Hence, the present review is intended to address the current challenges, recently recognized factors responsible for DM and DFU, their pathophysiology, insulin receptors associated with DM, medications in trend, and related complications.

1. Introduction

Diabetes Mellitus (DM) is one of the earliest identified diseases whose complications are well understood by humankind. Though it was initially described 3000 years back from Egyptian documentation, in the early 19th century, two major classes of DM were differentiated as Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) based on the absence of insulin or its reduced secretion [1]. Also, DM is a collection of metabolic disorders, which are complicated by defects/-complete absence in insulin (a peptide hormone) secretion (T1DM) or receptor damage resulting in low secretion (T2DM) of insulin [2]. When a patient fails to maintain the insulin level, it triggers other metabolic impairments (hypertension, cardiovascular disease, obesity), pathological conditions, and insulin deficiency/resistance. Studies reveal that T2DM is more prevalent than T1DM. A survey in 2018 among different epidemiology regions suggests that by 2030, 439 million people might get affected by T2DM due to modern food habits [3].

A literature survey from CDC (Center for Disease Control and Prevention, USA) states that only 10% of people are affected by this T1DM than T2DM. Further, the survey states that over 370 million are affected by T2DM. Other studies reveal that 80% of T2DM affected people live in developing regions of Asian and African countries. This is due to a sedentary lifestyle and food habits. Also, CDC projected that 10% of cases would rise from low-to-middle income and developing countries from the current stage. In the developed states of the US, T2DM will increase to 25.8 million, which is about 7.8% of the total population due

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to poor lifestyle and habits [4].

2. Types of diabetes mellitus

Two major types of DM are characterized based on the secretion or absence of insulin. However, few other DM subtypes are also identified and were not focused on them. T1DM (i.e due to autoimmune β-cell destruction) was identified as an autoimmune disease due to the complete absence of insulin or receptor damage since birth. Researchers identified this T1DM as a T-cell mediated acquired autoimmunity disorder. The other kind, T2DM, is described by insulin resistance, affecting insulin secretion. Compared to T2DM, T1DM patients were found with a low life span, and they were highly prone to cardio-vascular diseases (CVD) and severe metabolic conditions in their medical history [5]. The technological *vs.* scientific issue plays a significant role in discovering new technology or medicine to extend the life span of DM patients. This review is aimed to address DM and its complications and the techniques used to manage DM. Also, the types of drug delivery against DM are critically analyzed.

3. Major lifestyle factors and their effects on DM

Diabetes mellitus is observed globally in every country with a high prevalence, and its mortality rate is changing. The estimated data suggest that by the year of 2049, over 690 million people might get affected by DM due to the significant changes in their lifestyles. There is a notable increase in the % of the incidence of T1DM in 2020 than in 2019. Another survey says that children from 0 to 14 years of age have been affected, especially male children than female children [6]. In the modern world, people give importance to lifestyle habits such as smoking, alcohol, eating fat-rich junk foods (pizza, burger, white sugar-rich cakes, and fried foods), and thus ignore physical activity due to which they encounter T2DM around the age of 30–40 [7]. Extensive epidemiological study reports show that individuals following these lifestyle habits will become obese, and they are prone to the risk of being affected with T2DM. Several studies reported that about 30–60% of subjects with T2DM are identified with the associated disorder of obstructive sleep apnea [8]. Diet is another critical risk factor, but at the same time, the subject can overcome this risk factor and its associated T2DM. Obesity is reflected in the incidence of diseases in both developing and developed countries. The increase in T2DM among children and adults is associated with the widespread etiology of obesity [9]. The results obtained from the alcoholic subjects-directed clinical trials show that possible risk is directly correlated with insulin resistance in T2DM cases [10]. Some of the important risk factors, signs, symptoms and treatment for DM are presented in Fig. 1.

4. Pathogenesis of DM

In general, after a meal, there will be a rise in blood sugar level, which motivates insulin secretion, and subsequent generation of energy (ATP), which is transported, biotransformed or stored in muscles in the form of fat substances. The major portion of the triose-phosphate is converted into glucose and glycogen through gluconeogenesis. In the fed time, glucose arrives in liver *via* GLUT2, when blood glucose levels are high the excess glucose converts into glycogen through glucose-6-phosphate called glycogenesis. When glucose is needed as a source of energy in starvation time, glucagon is hydrolyzed by glycogen phosphorylase to generate glucose (glycogenolysis), which balances hypoglycemic conditions to immediate energy supplement to all parts of the body; which balances hypoglycemic conditions to immediate energy supplement to all parts of the body [11]. The pathophysiology of insulin and its associated biochemical conditions is depicted in Fig. 2. Fig. 2.a disclosed that GLUT2 is present in pancreatic β-cell. Blood glucose arrives pancreatic plasma membrane *via* GLUT2 transporter allows glucose to β-cells. The high concentration of glucose inside the cell, allows the beta cells to produce more ATP by glycolysis and cellular respiration, thus increasing the intracellular ratio of ATP to ADP inside β-cells. β-cells have potassium channels that are sensitive to this ratio. The increase of ATP causes these channels to close, causing a buildup of

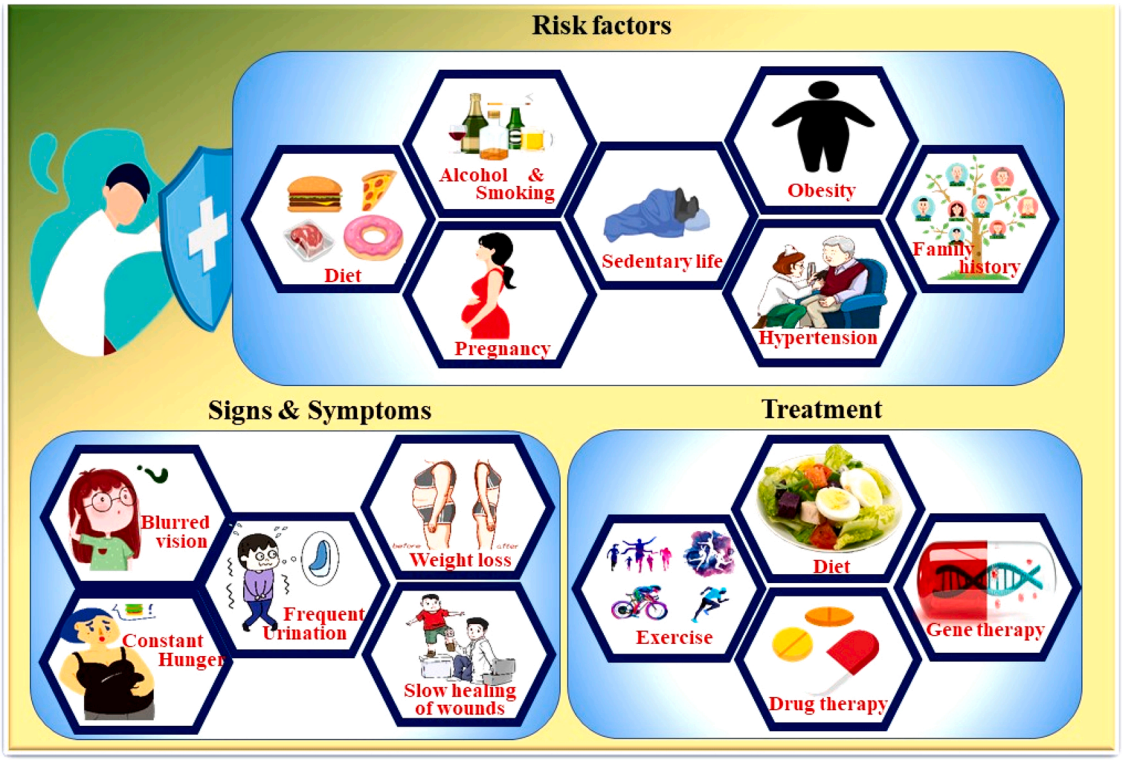

Fig. 1. Some of the important risk factor, signs & symptoms and treatment for diabetes mellitus.

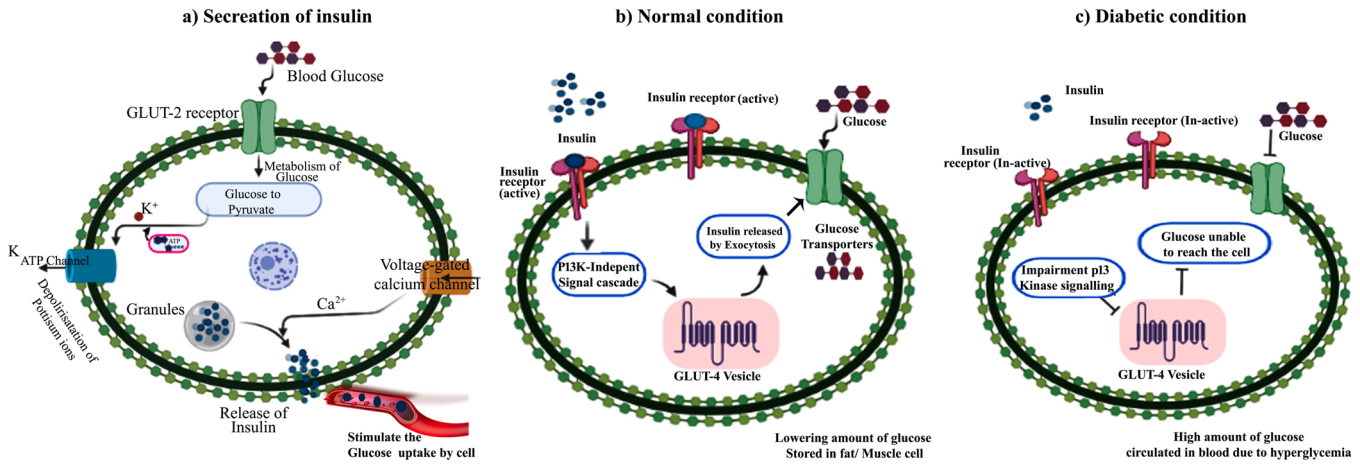

Fig. 2. The pathophysiology of insulin and its associated biochemical conditions in Type 2 Diabetes Mellitus. *Abbreviations*: KATP: adenosine triphosphate sensitive potassium; K: potassium; Ca^{2+}: Calcium^{2+} ions; PI3Ks: Phosphoinositide 3-kinases; GLUT4: Glucose transporter type 4.

potassium ions inside the cell and depolarizing the cell. This change in membrane potential causes voltage-gated calcium channels to open, allowing calcium to flow into the cell. Calcium triggers insulin granules to fuse with the plasma membrane, releasing insulin into the blood stream [12]. Fig. 2b sketches that insulin binds to insulin receptors, has activates IRS-1 in normal conditions. Then IRS-1 can activate PI3Kinase, which leads to phosphorylation and the activation of AKT thereby it stimulates GLUT2 pancreatic as well as GLUT4 translocation from cytosol to the plasma membrane and the glucose uptake from blood and maintaining normal glucose [13]. Fig. 2c highlighted that, DM is characterized by high blood glucose is the response to deficiency in insulin production by beta-cell/insulin resistance. The finding ways to increase PI3K/Akt activation due to dysfunctional insulin signaling in tissues [14].

There will be a complete absence or deficiency of insulin secretion by autoimmune damage on pancreatic β-cells in T1DM. Hence, it is identified as a metabolic conflict accompanied by T1DM. Finally, the damage in the β-cells symbolizes the onset of T1DM, thereby infiltrating white blood cells, specifically monocytes, lymphocytes along with pseudomorphic mixtures of somatostatin secreting glands and pancreatic glycogen polypeptide induced immunogens causing the impaired condition [15]. Autoimmune-altered genetic makeup by environmental toxicity is the reason for the destruction of islets of the β-cells. Another important type of T2DM occurs due to β-cell imbalance to take up glucose uptake and its regulation *via* insulin receptors. Multiple genetic and environmental factors are shown to be responsible for T2DM. Especially, obesity and high-fat diet cause defects in β-cells and peripheral tissue causing insulin resistance and glucose uptake/oxidize ability [16]. The pathogenic complications of DM are listed in Table 1.

As soon as multiple complications with DM are observed, the immediate step is to avoid the defined strategy. It is crucial to understand and overcome the fundamental stage of broad glycemic status and the associated disorder. The healthcare services will sort them out. In the 21st century, the new group of drugs such as sulphonylureas induce hypoglycemia and higher BMI, while metformin affects GIT and causes diarrhea, nausea, and lactic acidosis as side effects [17]. Some new-generation drugs (incretin, thiazolidinedione) also have similar side effects. In this regard, the scientific community is making continuous efforts to formulate a single or combined oral drugs/therapeutic agents to achieve glycemic control with limited side effects [18].

The current developments in therapeutics for DM and its combined management emphasize the immediate need for substantial investigations to identify potential drug delivery by natural products. Apart from allopathy, some other medications are also available as a natural supplement without formulation and pharmacological

Table 1
Metabolic and systemic complications of Diabetes Mellitus.

Metabolic complications	Long-lasting/Systemic complications
Diabetic ketoacidosis, Lactic acidosis	Neuropathy
Contagions	Amputation, cerebrovascular damage, dementia.
Hyper blood sugar, imbalanced osmotic pressure, non-ketonic coma, ketone bodies as a fatty streak	Atherosclerosis, cardiovascular damage, heart blockage, long term fat deposition in heart muscle
Fatigue, hazy vision, polyuria and polydipsia	Kidney damage leads to permanent renal dialysis, retinopathy, foot problems
Macrovascular diseases including stroke, altered blood pressure, vascular damage	Cataract, osteoporosis and blindness
Hyperlipoproteinemia	Women may have irregular periods and infertility
Diabetic foot ulcers	Gum diseases
Rhinocerebral mucormycosis malignant otitis externa, emphysematous pyelonephritis	Depression associated with a high risk of micro-macro vascular events

evaluation, like Siddha and Naturopathy. To regulate/control diabetes, insulin administration's modest and trouble-free passage is required, and still, it is a demand in the pharmacological drug delivery market [19]. Conventional drug delivery methodologies still have some limitations as well as side effects. The following regulations are still challenging: dosage fixation, the severity of glycemic index, low potency, and achieving the specific target. The same limitations are applicable for natural herbs or neutraceutical treatments given for DM [20].

5. Diabetic foot ulcer

Type 2 diabetics is a common metabolic disorder in those above 40 or middle-aged people. Diabetic foot ulcer (DFU) is an associated problem in those admitted in hospital for severe diabetics. While in treatment for DM, DFU is a common long-term complication, and its impact leads to noticeable morbidity and mortality. The ulceration/destruction causes infection in deep tissues accompanied by neurological aberrations in various conditions of peripheral arterial disease (PAD) of the lower limb of DM patients [21]. Under this condition, the protective layer of the skin gets infected by bacterial contamination while the epidermis layer starts to damage. Also, amputation is needed in diabetic subjects with DFU conditions to reduce infection in lower limbs. Recently, Diabetic Federation Control reported that 20–30% of the diabetic population were hospitalized for DF. In each year, 5% of the new diabetic case were increased, and out of 5%, 1% is reported for amputation for DFU. It has been noticed that every 20 s, a diabetic

patient is admitted for lower limb amputation [22,23]. In DFU, sensational loss in foot nerves is called diabetic peripheral neuropathy (DPN), and trauma is a substantially high-risk factor. Also, the above said were solely responsible for DFU, and it contributed to 90% of the cases admitted for foot ulceration related neuropathic problems.

However, the following factors of foot deformities, arthropathy, and previous foot ulceration were also listed for significant risk factors along with PAD and DPN [24]. In addition, the effect might be extended as a long-term defect due to diabetic retinopathy, nephropathy, poor diabetic management with uncontrolled glycaemic control, and high-risk factors associated with DFU. Recent statistical reports stated that the major cause of DFU is failure of managing their diabetic behavior by low-income people. Therefore, diabetic patients with poor hygiene, smoking and alcohol behaviors have above 20% chances of developing DFU [25,26]. Few studies state DM-associated DFU is relatively high in Europe and USA than in Asia. This is because of the traditional food habits for diabetic management, DPN and PAD by the Asians that reduce the chances of DFU and its associated amputation [27,28].

T2DM may give ways to develop various other complications like chronic glycemia, obesity, peripheral vascular disease and foot deformities. Hence, DM is not only the reason for DFU, whereas 90% of the DFU is developed by neuropathic-ischemic abnormalities associated with DM. Then the remaining 10% is affected by ischemic ulcers associated with DFU. Generally, DFU and its development in diabetic patients is explained by the following two metabolic pathways, 1. Autonomic neuropathy and 2. Peripheral sensor meter. Briefly, when the diabetic patients develop an infection in foot followed by hyper pressure in foot nerves, nerve deformities and inability to move foot, the chances of severe foot ulcers increase [29]. Alavi et al. (2014) did a simple case experiment. They found that increased plantar pressures during gait subsequently leads to foot ulceration in diabetic patients [30]. Literature reveals that the following factors such as high threat factors for foot ulcer patients with diabetic condition are as,

- ✓ Long-term type 2 diabetics (duration of disease).
- ✓ Prolonged kidney infection.
- ✓ Aging.
- ✓ Uncontrolled body mass index (BMI).
- ✓ Lesion in vision.
- ✓ Uncontrolled hypercholesterolemia & Hyperglycemia.
- ✓ Peripheral neuropathy.
- ✓ Trauma.
- ✓ Disturbances in joint movement due to uric acid deposition.
- ✓ Callus.
- ✓ Peripheral neuropathy.

With the above risk factors for DFU, diabetic foot lesion is a significant infectious factor in developing DFU. However, the foot lesion is classified depending on the minor to severe primary infection in the foot. In addition, diabetic foot lesion is graded and/or classified by the Wagner system, University of Texas system, and PEDIS system. Also, the above-said systems describe a few features of diabetic foot ulcer and classify them based on mild to severe site of infection, depth of ulceration, nerve infection and neuropathic infection leads to ischemia. The diabetic foot lesion is usually graded using the above systems from 0 (start of the lesion) to 5 (entire foot damage) by the medical practitioners [31]. Wagner-Meggitt system is one of the predominant systems, followed by almost all the practitioners with 0 (no risk) to 5 (high risk) grade classification. Briefly, grade 0 is no lesion in the foot; grade 1 is a lesion in the superficial layer, grade 2 is an ulcer in joint or in deep tissue, grade 3 is infection causes sepsis, grade 4 is gangrene and grade 5 is severe foot lesion in diabetic patients. Many classifications are available, but all are slightly modified from the Wagner system [32]. University of Texas system classifies the foot lesion into four stages A to D. Each stage has been further classified into four different grades depending on the presence of ischemia and/or infection or both of them in diabetic subjects. Infection in foot nerve/bones with ischemia was mainly seen in diabetic patients as per the University of Texas system [33].

Reviews state that supervision of DFU is quite critical, and a golden standard protocol is needed. Patients should be educated on DFU, foot lesion, glycemic control, proper care of injuries, diet control, and surgery. There are advanced products for wound care and few cost-effective therapies such as, negative pressure/Acupuncture wound therapy (NPWT), and hyperbaric oxygen therapy for DFU. However, since, low and middle-income country people fail to spend for these therapies [34], proper care for diabetic lesions is questionable in diabetic patients from low-income countries. Almost 50–80% of diabetic foot infections are inevitable. But proper footcare (washing, using anti-microbial cream when injured, use of TT, foot massage), diabetic control from hyperglycemic condition, and monthly or quarterly check-up for diabetic patients are useful in preventing DFU [35]. In addition, diabetic patients may increase DFU when their working environment involves/supports infection. So, the occupation of diabetic patients also plays a significant role in emerging DFU.

DFU patients should be cautious and keep an eye on their feet often, or on behalf of the patient, one family member must inspect the diabetic foot and take care of infected patients if the patient is aged. Regular foot examination is a special care in DFU. During the infection, irrespective of minor or major injury, it should be treated with care and monitored daily. Cleaning, dressing and applying creams or gentle treatment will help regrowth of tissue. The selection of footwear is also significant such that they trigger nerve impulses and blood circulation. Physician-prescribed footwear products (soft shoes, sandals, acupressure shoes) support treating callus or foot deformities. Apart from the care mentioned earlier, the physician's role in routine check-ups and following up the patient's condition, testing blood glucose level and frequent counseling about DFU care are essential [36,37].

Apoptosis/necrosis is a mutual process and inevitable in the cell cycle. In tissue injuries, necrotic debridement is essential in the injured tissue portion to treat inner tissues and bacterial infection. Debridement aids elimination of unwanted or affected tissue in infected places, callus formation, release from high pressure and growth of new tissues. Mechanical, biological, enzymatic, and surgical procedures are used for debridement. Mechanical debridement is a rare selective process. It is a manual method of eliminating necrotic tissue by hard wet–to–dry infection dressings that need a highly pressurized hydrotherapy process. Biological debridement is a type of sterilization process. It has also been reported that biological debridement is an apt and successful procedure in removing pathogens while it kills healthy tissues during sterilization. Enzymatic debridement uses enzymes as an agent to kill necrotic tissue. When compared to all the open debridement, enzymatic debridement is a successful method in killing necrotic tissue without affecting healthy cells-however, a little expensive method for treating ulcers. After debridement, stem cell therapy is an emerging and advanced strategic therapy to cure DFU. Preliminary results show stem cells therapy indicates a promising effect against DFU. Overall, DFU is a controllable infection when injured diabetic patients are given proper hygiene care [38,39].

6. Current therapeutic approaches for DM

Diabetes mellitus is a disorder with no known/effective treatment and is highly prevalent worldwide. According to World Health Organization (WHO) data, 387 million people aged between 40 and 59 years from low- and middle-income underdeveloped/developing countries face this DM as a significant severe killer disease and a threat to humans [40]. In general, selection of medicine to treat diabetes, based on reducing or monitoring lowering glucose level and its associated types of therapy is dependent on a list of factors, such as the severity of the glycemic condition, BMI, the capability of monitoring blood glucose level and selection of cost of the prescription [16].

So far, over six decades, the majority of the research works reported that the therapeutics/treatment for T1DM would involve the stimulation of insulin secretion by Glucagon-Like Peptide (GLP) equivalents such as exenatide and liraglutide by compensating β-cell imbalances as well as most extended survival of islet cells through direct insulin injection while inhibiting dipeptidyl peptidases-4(DPP-4) [41]. Also, these GLP analogs aim to regenerate islet cells by islet neogenesis associated protein (INGAP) peptide therapy [42]. This will aim at islet cell regeneration, which is surrounded by other cells. As that of Type 1, the therapeutic approach for T2DM also contains predictable therapeutics, such as sulfonylureas (enhance insulin discharge), troglitazone (raises the insulin function against excess fat stored in the muscle), metformin (acts on insulin mechanism by oxidizing liver tissue glucose, and some of the acarbose) and miglitol (lowers the absorption of the carbohydrates from meals) [43].

We have discussed the allopathic medications and their actions on insulin management and their secretion by β-cells in both T1DM and T2DM. Clinical trials reveal that these drugs are widely used to manage/control the uncontrolled blood glucose levels and associated T2DM with certain limitations and significant side effects. On the other hand, some medications have some strategies for insulin secretion stimulation when prescribed with combinational oral therapy (sulfonylureas) [44]. Another vital drug is metformin, approved by Food and Drug Administration (FDA) and it also prescribed as a combinational drug to manage DM, insulin level and BMI. Like metformin, troglitazone is also used for combined insulin therapy, actively controlling hyperglycemia and its management [45].

6.1. Role of Medicinal plants for the treatment of DM

Diabetes mellitus can cause many neuro- and nephrological imbalances. There are numerous types of glucose/insulin balancing/monitoring drugs identified as anti-diabetics with diverse mechanisms. Also, those different mechanisms must stimulate insulin secretion to increase

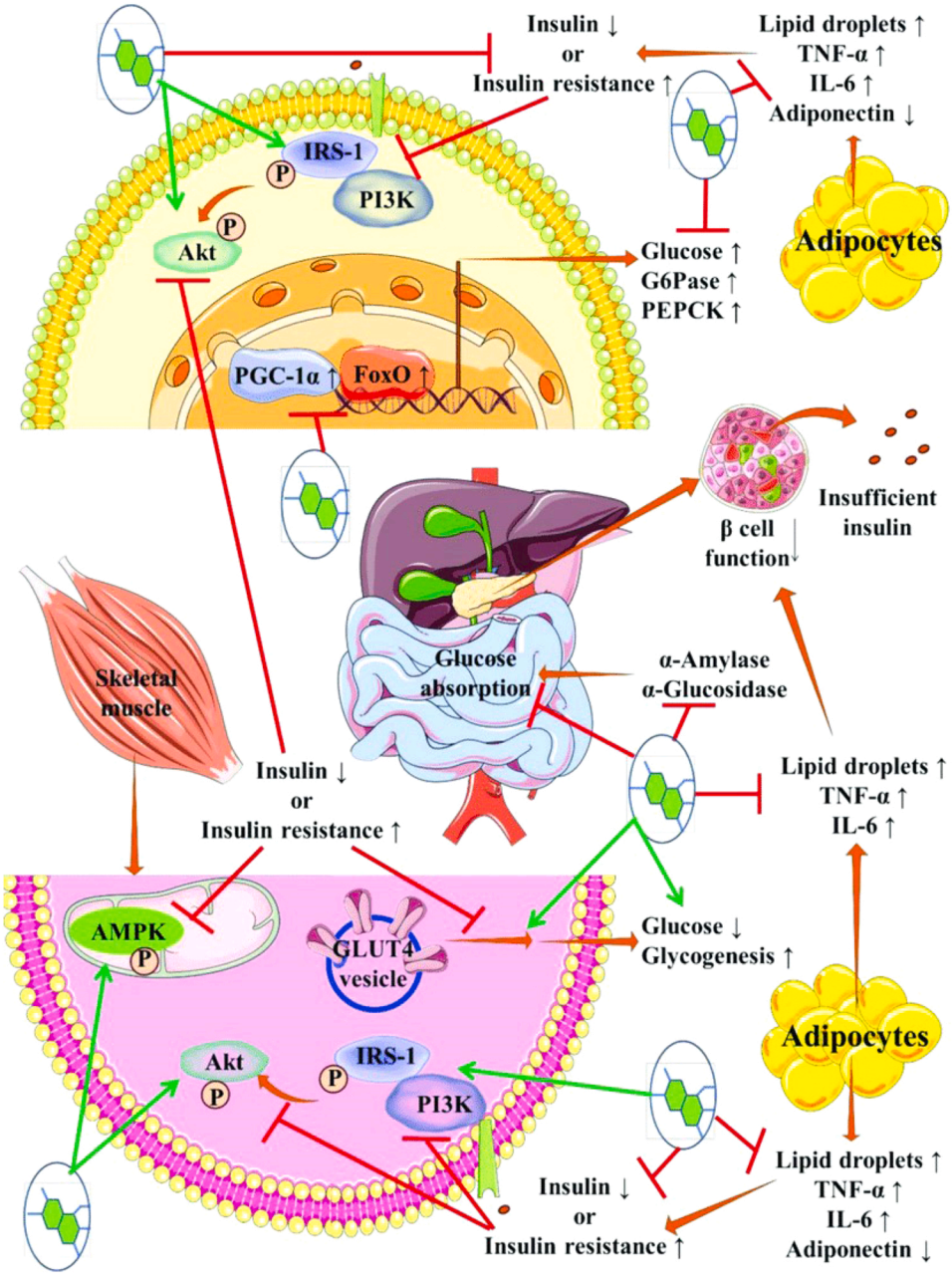

Fig. 3. Multiple therapeutic targets of plant secondary metabolites in diabetes management. Multiple therapeutic targets of plant secondary metabolites in diabetes management [50]. *Abbreviations*: IRS-1: insulin receptor substrate 1; P3K: PI3K: phosphatidylinositol 3-kinase; AKT: ak strain transforming; PGC-1α: peroxisome-proliferator-activated receptor-γ coactivator-1 alpha; FoxO: forkhead box O; AMPK: adenosine monophosphate-activated protein kinase; PI3Ks: phosphoinositide 3-kinases; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; glucose 6Pase: glucose 6-phosphatase; PEPCK: phosphoenolpyruvate carboxykinase.

peripheral absorption of glucose from the intestine. After over three decades of research, a substantial development was made by numerous anti-diabetic drugs to maintain insulin levels, although with some disadvantages [46]. Advanced research was also tried with medicinal plants as the best sources as they are cheap, readily available, toxic-free with zero side effects. The medicinal plants are rich in flavonoids, terpenoids, alkaloids, glycosides, and carotenoids, which can facilitate the management of DM. These antioxidant and anti-diabetic activity-rich medicinal plants can improve pancreatic hormone secretion, absorption of intestinal glucose, and energy utilization [47,48]. Nowadays, people with diabetes choose natural medicinal plants with the above-mentioned antioxidant properties to reduce side effects and associated risks. Since medicinal plants have less-toxic ingredients (tannins, phenolic compounds and catechins) with almost zero side effects, there is a continued interest in using them as a possible treatment for DM. These hypo-glycemic herbs enhance insulin secretion, increase glucose absorption, aid the oxidization of excess muscle fat, and prevent glucose synthesis in liver cells [49]. The detailed graphical representation of multiple therapeutic targets of plant secondary metabolites in diabetes management is presented in Fig. 3 .

6.2. Nanoparticle-based therapeutic approach in DM

Nanotechnology aspects have been applied in some of the recent advanced research. Nanoparticle-based drug delivery for diabetes has been proved efficient with fewer side effects. Novel probes can be introduced through nanoparticles to monitor blood glucose *via* insulin delivery [51]. Nanoparticle-mediated drug delivery is a promising tool that can approach the target. The pores in the delivery systems are noticeably large, giving passage to small molecules like oxygen, glucose, and endocrine molecules [52]. Meanwhile, it will allow enough small molecules along larger immunoglobulins of immune cells to maintain the immune system against pathogenic microbes. In nanoparticle-based drug delivery, microcapsules have replaced Langerhans islets, which are commonly imitated from pigs, which may have a chance for less skin allergy to diabetes patients. This treatment will help avoid high immunosuppressants with harmful side effects [53]. Some of the important nanotechnology-based treatment methods of DM are presented in Fig. 4.

One of the significant advantages of this nanoparticle-mediated drug delivery is that it will not allow the patient to enter the severe condition and associated serious infections. It has enormous benefits, including enhanced bioavailability of drugs at specific organs, tissues, and tumors with high mass dosage to act on the target site directly. Every technology has some drawbacks, and here the stability is the biggest challenge in the three-dimensional nanostructures to two-dimensional layered nanosurfaces. Also, the protocol is yet to be standardized for easy manufacture. With additional concern, this nanoparticle drug delivery and exposure can become toxic or hazardous when the nanomaterials such as carbon buckyballs and nanotubes are inhaled, ingested, or absorbed through the skin. But compared to traditional drug delivery treatment for T1DM and T2DM the insulin delivery is painless. Conversely, recent micro and nano-drug deliveries have facilitated the regulated insulin administration and its delivery [54].

6.3. Green synthesized nano-drug delivery for DM

Plants are cheap and easily obtained sources with enough medicinal properties. Medicinal plants are rich in antioxidants and exhibit anticancer and anti-diabetic activities [55]. Although plants can easily fuse with other compounds, plant-derived nano drug-mediated delivery systems are considered superior. Phytocompounds isolated from plants are given immense importance as alternative medicine [56,57]. At present, the FDA has approved nearly 50% of the anti-diabetic drugs, which were plant-derived phytocompounds or their derivatives. Several research groups are working on medicinal plant-mediated or green synthesized nano-drug discovery, and some of them have entered the market [58,59].

Additionally, 1200 medicinal plants have been approved to have anti-diabetic activity by the FDA. Without documentation, more than 15,000 medicinal plants are used as anti-diabetic drugs in rural areas worldwide. Those undocumented medicinal plants are taken as oral drugs with zero side effects. Drug delivery research has improved considerably with anti-diabetic phytocompounds [60]. Also, improved enzymatic digestion from GIT with improved pharmacokinetics and pharmacodynamics profile was obtained even with a lower drug dose [61]. Drugs are encapsulated in a nano polymeric membrane called

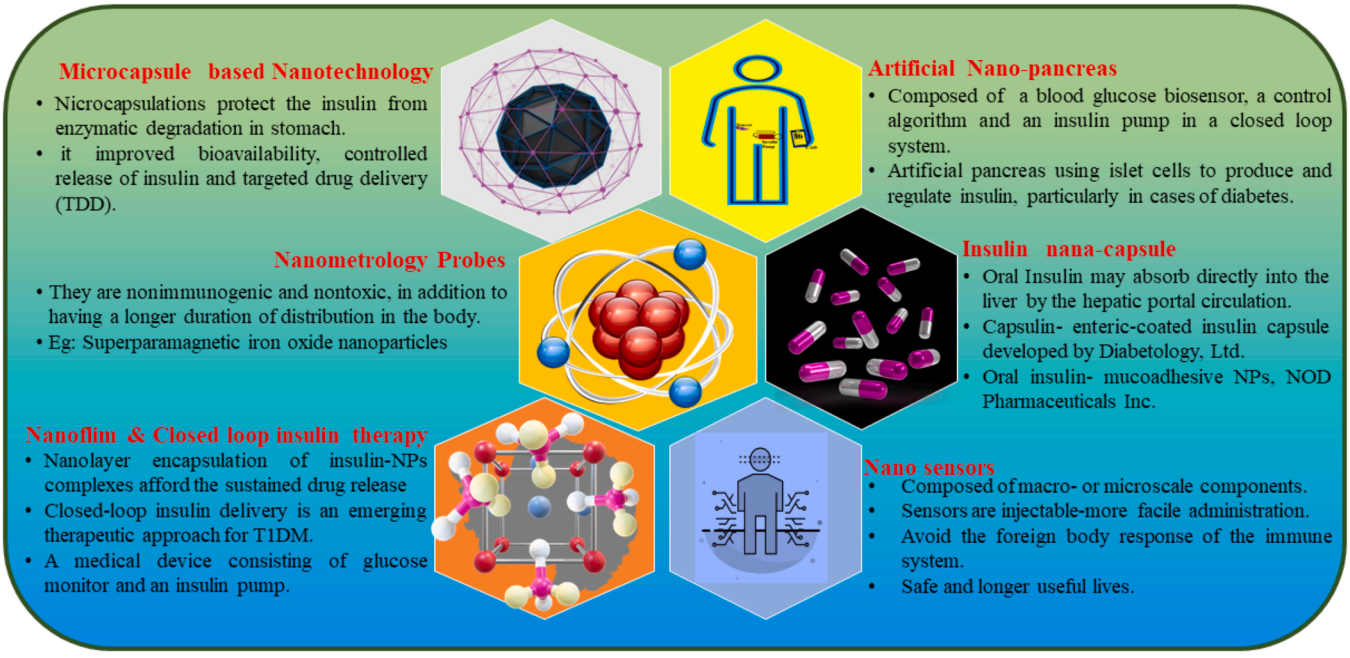

Fig. 4. A different aspect of nanotechnology-based screening and treatment strategies of DM. *Abbreviations*: TDD: target drug delivery; T1DM: Type 1 Diabetes Mellitus; NPs: nanoparticles.

nanocapsules or nanospheres. Polymers are deemed most important in nano-delivery systems because of their flexibility, functionalization, and various molecular synthesis [62]. In the recent past, different kinds of nano formulations were prepared from medicinal plants for the treatment of DM against both T1DM and T2DM (Fig. 5).

In anti-diabetic drugs, phytocompounds have potential function with low/zero side effects [63,64]. The *British Medical Journal* declares that phytocompounds are linked to four hypoglycemic mechanisms in diabetes treatment. This includes phytocompounds that help reduce carbohydrate breakdown and its absorption and digestion while allowing energy metabolism. Hence, this will improve endocrine and liver metabolic rates, antioxidant, and anti-inflammatory functions [65]. Oral route drugs have some critical defects if the medicines are anti-diabetic phytocompounds. Phytocompound-mediated oral nano-drug delivery is used to treat T2DM. The following advantages were observed when phytocompounds were used in anti-diabetic therapy in animal trials [66].

- Phytocompound-mediated nano delivery mechanisms helps to improve the strength of the drugs and scavenge them from enzymatic free radicals from GIT secretion.
- Nano drug delivery improves the pharmacodynamics and pharmacokinetics of molecular-level systems, which help increase the cellular drug influx. *E.g.* P-glycoprotein.
- The intestinal lymphatic system avoids the first-pass effect. Hence, this nano-drug delivery can enter lymph through the lymphatic system with the help of Mast cells, increasing the systemic circulation.
- Above all, nanocarriers achieve targeted drug release by controlling and avoiding the opsonization of drug release [67].

With these advantages, phytocompounds indicate better anti-diabetic ability with improved bioavailability, less toxicity, and specific target site even with low dosage. A recent study reveals that naturally formulated hyaluronic acid can be used as a beneficial drug for T2DM. The most critical point is that the materials used for nano-drug deliveries are from inorganic or synthetic chemical , and their preparation is tough or mostly chemical processed. Some materials are obtained from natural sources but processed with an organic chemical. So, it might be half-synthetic. The experiments conducted with clinical and animal models have some limitations when taken into molecular studies [68].

6.4. Chemical mediated nano-drug delivery for DM

Chemical-mediated or synthetic nanocarriers are extensively used nowadays in the management of DM. Various types of therapeutics are followed to treat diabetes. But the side effects/infection associated metabolic disorders are extensive. Also, patients feel pain due to infection caused by daily insulin injection when diabetes is uncontrolled. So, to avoid those complications [69], a carrier with nanosized material can carry insulin without painful injections. The next-generation diabetic therapeutical management of different forms of insulin-based nano--formulation is depicted in Fig. 6. These nanoparticles are synthesized from polysaccharides, synthetic polymers, and lipids. This nano-mediated drug delivery aims to improve homeostasis and drug stability and achieve 100% bioavailability. A type of synthetic polymer called PLGA is branded for its quick biodegradability and biocompatibility and is recognized as a popular polymer used in the management of DM [70]. Once an insulin-phospholipid complex is made, it is transported with PLGA by reverse micelle-solvent evaporation. When the nanoparticles reach the stomach, they are digested by acidic digestive enzymes. There would be no injury or rupture of the insulin molecule during this procedure, as evidenced by numerous *in vivo* studies [71]. Generally, PLGA nanoparticles are negatively charged. Hence, they have a low permeability with a mucus layer, and can cross the cell membrane easily. Polylactic acid, polyallylamine (PAA), penetratin, niosomes, poly (amidoamine) dendrimers, polymeric micelles, PEG-PE, Eudragit-based nanoparticles, and some of the inorganic nanoparticles are extensively used in nano-drug carriers [72]. Besides these synthetic nanoparticles,

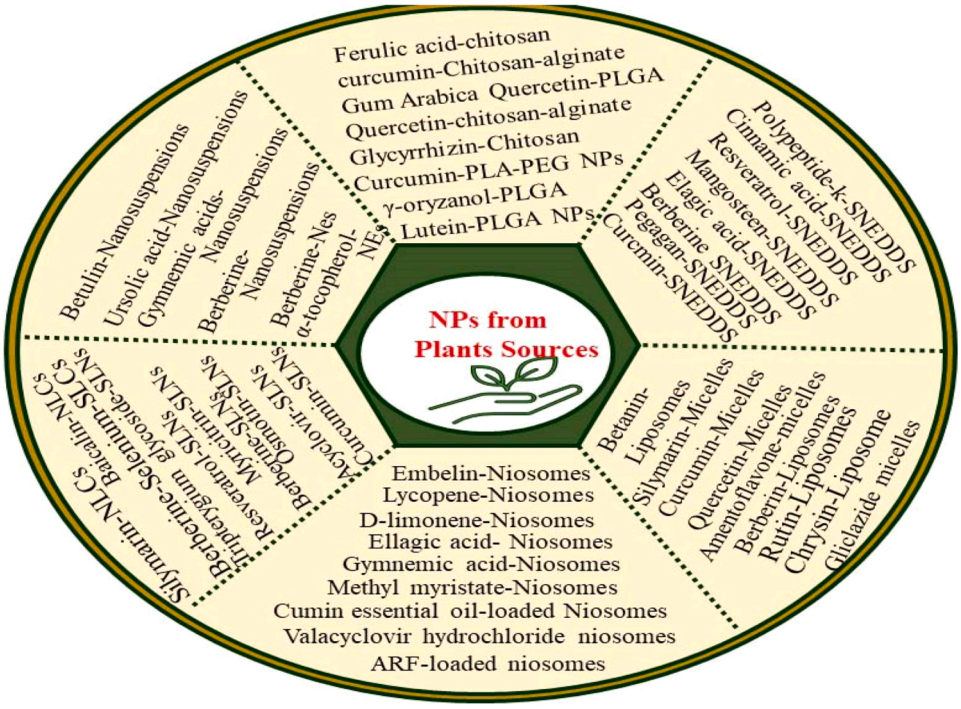

Fig. 5. Different type of plant-based nanoformulation against the treatment of DM. *Abbreviations*: PLGA: poly D,L-lactic-co-glycolic acid; PEG: polyethylene glycol; NPs: Nanoparticles; SNEDDS: self-nanoemulsifying drug delivery system; ARF: alkaloid rich fraction; NLCs: nanostructured lipid carriers; SLNs: solid lipid nanoparticles, NEs: Neosomes.

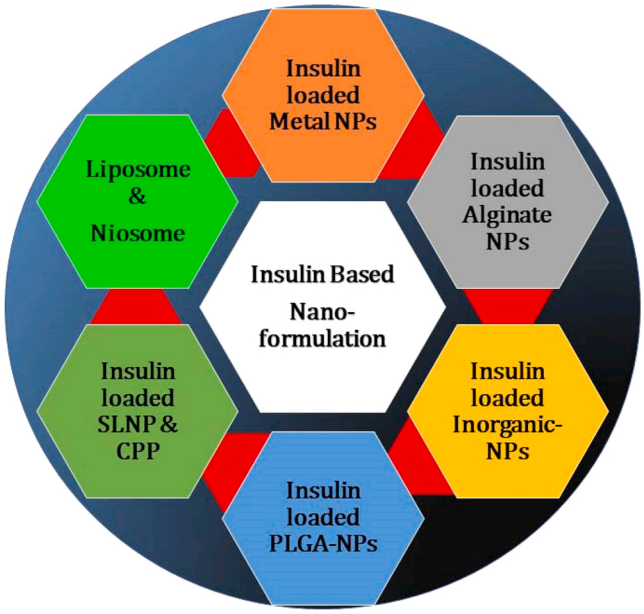

Fig. 6. The next generation diabetic therapeutical management of different form of insulin-based nanoformulation. PLGA: poly(lactic-co-glycolic acid); SLNP: solid-liquid nanoparticles, NPs: nanoparticle; CPP: cell-penetrating peptides.

metal-coated synthetic and green synthesized nanoparticles also play a significant role in drug delivery against T2DM. Silver, gold, and superparamagnetic material-coated nanoparticles are used in insulin management [73]. Anti-diabetic activity of different NP formulations with their mode of action and possible involvement of carbohydrate metabolic pathway are presented in Table 2.

For example, some *in vivo* studies have reported alginate-bead coated (anionic polysaccharide) nanoparticles in glucose-lowering. Colloidal gel-coated gold, silver, and superparamagnetic particles play a significant role in targeted drug delivery. Nanoparticles are also used extensively in glucose monitoring management. Precise and regular blood glucose monitoring is essential in the control and management of DM. But it is acknowledged that frequent blood collection with painful needles or sticks is considered dangerous or a nuisance to check clinical glucose with the presently available testing. Hence, glucose sensors capable of quantifying glucose accurately without pain were developed [110]. Also, this procedure can be done in-home without diagnostic specialists. Patients widely use nano chip-based glucose-sensing Accu-check glucometers at home. Even though certain limitations and negative feedback are raised in nanoparticles-mediated drug delivery, extensive research is needed to sort these issues [111].

7. Gene therapy

According to researchers, several gene mutations have been related to an increased risk of DM. In general, mutations in any gene involved in glucose regulation may raise the risk of developing T2DM. These include genes that control the production of glucose, the production and regulation of insulin, and sensing of glucose levels in the body. Mitochondrial genome mutations are denoted as mitochondrial diabetes. This is also known as MELAS syndrome (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes).

Recent anti-diabetic clinical trials and their involved models have exposed that hypoglycemic insulin drugs or insulin injections or analogs can give just a temporary effect to minimize hyperglycemic impact, and there is no improvement on the islets of β-cells of insulin maintenance of blood glucose homeostasis and avoiding various illnesses [112]. It is challenging to admit exogenous drug administration and to mimic the complications. However, the insulin injection systemic pathway is somewhat changed from the endocrine pancreatic islet of β-cells. Gene therapy states that exogenous gene transfer into suitable beneficiary cells of patients can provide a complete remedy to specific diseases [113]. Gene therapy is an optimistic approach to treating diabetes. It targets the main causative substances that were arrested or sent back to their original condition. In this therapy, DNA, small interfering RNA (siRNA), mRNA, microRNA, and some antisense oligonucleotides are used as the primary genetic drugs [114]. Also, this is divided into immune gene therapy, replacement gene therapy and regulatory gene therapy.

7.1. Immune gene therapy

This type of gene therapy might be started in patients with T1DM. The current approach regarding this therapy attempts to stop or reverse an autoimmune response to target genes. These target genes protect the islet cells. IL-10, an anti-inflammatory cytokine with various biological signaling and functions with immune response, is highly expressed with Type 2 MHC antigens [115]. Th1 and Th2 cells are chronic immune cells that overcome the autoimmune antigens that produce autoimmune disease. In a study, rAAVIL-10 (intramuscular recombinant adeno-associated viral vector endocrine murine IL-10) was administrated into non-obese diabetic mice and found 60% of non-obese diabetic mice injected with higher-dose rAAVIL-10 maintained euglycemic condition until 117 days. On the contrary, the mice administered with low dose rAAVIL-10 could not hold diabetes for at least 17 days. Coleman et al. (2016) documented that immune precursor-mediated gene therapy diminishes the destruction of pancreatic cells while restoring the long-term tolerance of islet cells against its antigen by memory T cells [116]. It concludes that IL-10 gene expression positively affected reducing autoimmunity [117]. So, immune precursor-mediated immune gene therapy could be an interventive immunotherapy against T1DM.

7.2. Replacement gene therapy

As per various reports, various damage factors are responsible for the damage β-cells of islets of pancreatic cells in patients with T1DM and T2DM. Also, non-β-cells can secrete insulin that can replace the damaged pancreatic β-cells. Hence, successful replacement gene therapy must fulfill the following conditions.

- It should be an active/actual insulin gene transfer system.
- It must be managed with the regulatory mechanism by controlling blood glucose levels and insulin elevation by islet cells.
- Those replacement-involved cells can secrete immature proinsulin until it reaches β-cells to be active and mature insulin to meet the target.
- The replacement gene on target cells should have with same biochemical function as β-cells, and significantly, it should not be attacked by the autoimmune system [118].

RNA viral vectors such as adeno associated-virus, lentivirus, and non-liposomal vectors of liposomes and plasmids have been used as replacement genes in the tissues/liver, pancreas, GIT, and endocrine K cells. Many studies have been carried out with transgenic mice induced STZ. After, STZ GIP promoter transfers the insulin as replacement gene therapy to K cells to GIT, euglycemia will be achieved. It shows that K cells can be a better replacement and have the potential to secrete enough insulin while maintaining blood glucose homeostasis and energy supplementation [119]. In 2015, Romer and Sussel treated STZ-induced non-obese diabetic mice and dogs with adeno-associated viral vectors that carried insulin replacement gene therapy from glucokinase genes into skeletal muscle cells. These two genes enhanced the insulin level by translocating GLUT4 and glucokinase by transport glucose to muscle cells. Generally, glucokinase will play as a 'glucose sensor.' It is essential

Table 2
Antidiabetic activity of different NP formulations with their mode of action and possible involvement of carbohydrate metabolic pathway.

Nanoformulation	Experimental model	Mode of action	Possible involvement of metabolic pathway	Refs.
Vildagliptin -gold and silver NPs	In vitro DPP-IV inhibitory activity	Augment the stability, extend the drug release, increase the glycaemic level in the postprandial conditions	DPP-IV inhibitory pathway	[74]
Wedelolactone-AuNPs	RIN-5F	Reduce lipid peroxidation, improve the antioxidants status and insulin secretion	GLUT2 signaling pathway	[75]
L. japonica-AgNPs	In vitro assay	Inhibit the α-amylase and α-glucosidase	Inhibition Polysaccharide digestive enzymes	[76]
W. somnifera-PtNPs	STZ induced diabetic in Sprague-Dawley rats	Reduction in plasma glucose	Improve insulin signaling cascade mechanism	[77]
H. sabdariffa-SeNPs	STZ induced diabetic rats	Improve the serum testosterone, reduce the oxidative stress	Conceivable involvement of Nrf2-keap1 signaling pathway	[78]
CuNPs	STZ induced diabetic rats	Prevent the cardio-vascular structural and functional defects, Increased bioavailability of NO in the endothelium and reduced the oxidative stress	May be the participation of PI3K–Akt–eNOS signaling pathway	[79]
AuNPS	Human foreskin fibroblasts & STZ induced BALB/c mice	Decreased RAGE expression, normalize the antioxidant and angiogenesis system	AGE-mediated RAGE vascular complications Mechanism	[80]
ZnONPs	STZ induced diabetic rats	Enhance glycaemic condition, improve the inflammatory changes, renewal of islets of Langerhans and increased insulin-secreting granules.	Nrf2-keap1 signaling pathway	[81]
ZnONPs	STZ induced type 1 diabetic rats	Improvement of renal function, inhibition of renal fibrosis, oxidative stress, inflammation, regulation the abnormal angiogenesis, amendment of podocyte injury.	JAK/STAT signaling mechanism	[82]
Amino acid-functionalized gadofullerene NPs	Db/db diabetic mice	Regulate the pancreas dysfunctions, reduced oxidative stress and inflammation, retaining glucose and lipid metabolism	IRS2/PI3K/AKT signal pathway	[83]
SLNs from *P. acacia* and *P. curviflorus*	HFD-STZ induced diabetic rats	Reduce blood glucose, insulin resistance, decreased lipid peroxidation (malondialdehyde), boost up the endogenous antioxidant system	Nrf2-keap1 signaling pathway	[84]
SLNs-*F. religiosa*	STZ & fructose induced diabetic rats	Noticeable hypoglycaemic and insulin-sensitizing effects	IRS/PI3K/AKT/GLUT4 signaling pathway	[85]
Ferulic acid-chitosan NPs	STZ induced diabetic rats	Enhancement body weight, decrease in blood glucose level along with a regulatory effect on blood lipid profile	AMPK/SREBP-1c Signaling Pathway	[86]
Quercetin-PLGA-NPs	STZ induced diabetic rats	Enhance the oral therapy by minimizing the dose and dosage frequency	Possible involvement of insulin signaling cascade mechanism	[87]
Chitosan/alginate/ maltodextrin/pluronic-microparticles	STZ induced diabetic rats	Reduce the elevated blood glucose level and lipid profile (total cholesterol, triglycerides, HDL cholesterol). Maintain the body-weigh and speed up the wound healing mechanism	AMPK/SREBP-1c Signaling mechanism	[88]
Ursolic acid-Nanosuspension	STZ induced diabetic rats	Remedial action on pancreatic toxicity decreases hyperglycemia and reducing elevated oxidative stress.	Nrf2-keap1 signaling mechanism	[89]
Berberine-Nanosuspension	STZ induced diabetic in C57BL/6 mice	Decreases blood glucose and improves lipid metabolism	AMPK/FoxO1/mTORC1/SREBP-1c Signaling Pathway	[90]
Sesamol-PLGA-Nanosuspension	HFD-STZ induced type-II diabetic rats	Diminished the TNF-α levels in wound tissue and enhanced collagen deposition. Regulate the HSP-27, VEGF ERK, and PDGF-B expression. Speed up the re-epithelization, fibroblast migration, collagen deposition and reduced inflammatory cell infiltration	Inhibition of PI3K/Akt/mTOR signaling pathways	[91]
Psidium guajava	HFD-STZ induced type-II diabetic rats	Retrieve the blood glucose level, recover the hepatic and renal damage	AMPK/FoxO1/mTORC1/SREBP-1c Signaling Pathway	[92]
Lycopene-Nanosuspension	NIDDM in diabetic rats	Alleviate the cholesterol, triglycerides, LDL, HDL, VLDL, and antioxidant corresponds	AMPK/SREBP-1c Signaling mechanism	[93]
Eudragit-Nanosuspension	Nicotinamide-STZ induced diabetic rats	Rapidly reduced the blood glucose with Superior pharmacokinetic effects	Possible involvement of insulin signaling cascade pathway	[94]
Silymarin-nanostructured lipid carriers	Caco-2 cellline, HFD-STZ induced diabetic mouse	Considerable down-regulation of blood glucose and lipid profile, especially in triglyceride level	AMPK/SREBP-1c Signaling pathway	[95]
Nanostructured Lipid Carriers of Pioglitazone	3T3-L1 cellline and Wound healing model in Wistar albino rats	Neutralize the inflammation process and decrease MMP-9 expression	Possible inhibition of Proliferation, Angiogenesis and Remodeling of diabetic wound	[96]
Nanostructured Lipid Carriers of EGF and curcumin	NIH 3T3 and HaCaT cellline	Speed Up the wound closure mechanism and boost up the antioxidant enzyme	Nrf2-keap1 signaling pathway	[97]
Phenytoin Loaded Nanostructured Lipid Carriers	Diabetic Foot Ulceration in human	Strengthen the skin penetration mechanism	Keratinocyte Protein Signaling pathway	[98]
Baicalin-loaded nanostructured lipid carriers	HFD-STZ induced diabetic rats in Sprague-Dawley	Regulate the fasting Blood Glucose, Glycosylated Hemoglobin level, regulate the lipid metabolism	AMPK/SREBP-1c Signaling pathway	[99]
Thymoquinone-Loaded Nanostructured Lipid Carrier	In Vitro Wound Healing Models in (NIH/3T3 and 3T3-L1	Stimulate the fibroblast proliferation and migration, diminish the nitrosative stress, decreasing the apoptotic process, increasing cell proliferation and lowering the ROS levels	Nrf2-keap1 signaling pathway	[100]
Lycopene-Niosomes	Alloxan induced diabetic rats	Decrease the blood glucose, diminished the T cell-dependent adaptive immune response, expanding the total antioxidant function	Nrf2-keap1 signaling pathway	[101]
Berberine-Niosomes	Caco-2 cells, HFD-STZ induced diabetic mice	Reduced the blood glucose level, reduces the P-glycoprotein efflux of BBR and improves its permeability	MAPK/ERK signaling pathway	[102]

(*continued on next page*)

Table 2 (*continued*)

Nanoformulation	Experimental model	Mode of action	Possible involvement of metabolic pathway	Refs.
Embelin-niosomes	STZ induced diabetic rats	Increases in SOD, CAT, and GSH, decline the lipid peroxidation level	Nrf2-keap1 signaling pathway	[103]
Pioglitazone-niosomes	STZ induced T2DM in diabetic rats	Reduction in glucose levels	Possible involvement of insulin signaling cascade mechanism	[104]
Gymnema sylvestre-niosomes	Alloxan induced diabetic rats	Reduced the blood glucose level, improved the anti-hyperglycemic activity	IRS/PI3K/AKT/GLUT4 signal pathway	[105]
Fumaria officinalis-Niosomes	Alloxan induced diabetic rats	Boost up the anti-inflammatory gene (IL-10), improve the pro-inflammatory gene expression (TNF-alpha, IL-6) ameliorate the oxidative-stress	Immunomodulation/reverse relationship between inflammation and insulin stimulation	[106]
Amentoflavone-Micelle	KKAy Mice	Lowering blood lipids, reducing inflammatory responses	PPAR γ, PI3K/Akt signaling pathway	[107]
Silymarin-pluronic nanomicelles	STZ induced T2DM in diabetic rats	Improve the status of anti-hyperglycemic, anti-hyperlipidemic and antioxidant status	Nrf2-keap1 and AMPK/SREBP-1c pathway	[108]
Betanin-liposomes	STZ induced diabetes nephropathy	Decreased the blood glucose and body weight, enhanced the serum insulin level, regularize the hyperglycemia, oxidative stress, hyperlipidemia, and lower the tissue damage	Nrf2-keap1 and IRS/PI3K/AKT/GLUT4 pathway	[109]

STZ: Streptozotocin; T2DM: Type 2 diabetes mellitus; HFD: High fat diet; NIDDM: Non-insulin-dependent diabetes mellitus.

to key regulatory enzymes that regulate the insulin hormone as per blood glucose concentration requirement [120].

7.3. Regulatory gene therapy

Initially, all biosynthesis processes are regulated by a set of programmed procedures with programmed genes [118]. From the start of the synthesis through the maturation of pancreatic β-cells to the destination of insulin secretion, many cytokines are involved in the regulation. Hence, researchers attempt to transfer the genes that encode interrelated cytokines to the organism. This process will normalize insulin secretion, and the blood glucose level will be regulated. IGF1 (insulin-like growth factor-1) is a β-cell mitogen that will stimulate amino acids and glucose absorption from GIT. Further, it will control the excess of glucose into glycogen and balance the insulin burden to lifestyle. IFN-beta, AAV8, and AAV-IGF-1 genes are the best suited for regulatory gene therapy, which have an excellent therapeutic prospective for type 1 diabetes [121]. Apart from gene therapy, chemical- and green synthesis-mediated nano-drug delivery, nutrition therapy, and stem cell phage therapy are also involved in the treatment/control of diabetes [122]. Some of the important gene therapy methods employed in the clinical management of DM is tabulated in Table 3.

8. Diabetic wound therapeutics in trends

In general, the ability to tolerate a long-term wound is a critical issue. Wound healing is also slowed down in alcoholics, the elderly, and people with metabolic disorders, blood clotting problems, and diabetes. Among all, diabetic patients and their injuries and wounds significantly impact healing, which may take extended period. According to an IDF report, more than 500 million new diabetic patients will be added in the coming decade. As a result, the world requires rapid recovery from diabetic wounds to avoid other diabetic complications or keep people with diabetes alive. Various treatments with various approaches have been developed to treat diabetic wounds. The systemic delivery method is commonly used, for example, when prescribing drugs to diabetic patients, the drugs enter the bloodstream. However, there will be severe/causative side effects if wound treatment is not provided [134].

On the other hand, indigenous people use natural/topical treatments such as herbal, plant, and massage to reduce side effects. Nonetheless, these approaches are insufficient for treating diabetic wounds. Furthermore, both treatments are time-consuming and have a delayed response to injuries. According to the literature, bioengineered grafts, growth factor therapy, synthetic hydrophobic polymer dressings, natural polymer therapy for unwanted allergic conditions, and foam dressing are all used to treat diabetic wounds [135]. However, no effective treatment/therapy is currently available for effective diabetic wound dressing without side effects. Only a few reports claim to treat diabetic wounds with diabetic foot ulcers effectively, but those have failed.

9. Nanotechnology *vs.* diabetic wound

Drug delivery through nanoparticle/nanomaterials-based diabetic wound healing treatments shows some benefits in reducing side effects or quick wound healing. Nanoparticles act as drug delivery systems with controlled drug release. They have also been reported to have anti-cancer, anti-diabetic, anti-microbial properties [136]. It has already been well demonstrated that nanoparticles treat damaged tissues by stimulating cell proliferation, migration, microbe inhibition, thereby controlling wound healing [137].

Recently, 3D polymer hydrogels have been used in tissue engineering and drug delivery. Hydrogels with high water content, expanded elasticity and biocompatibility have reaped success in this regard. It has been discovered that nanoparticles collaged with hydrogels exhibit controlled drug release and localization in wound burst and structural remodeling and localization [138]. Meanwhile, according to another report, characteristic nanofibers tuned mechanical properties and increased pore size and surface area through chronic wound control [139]. AgNPs have been used as an anti-inflammatory agent against burns, chronic ulcers, tissue regeneration, targeted drug delivery, and collagen installation for chronic diabetic wounds in detail. Non-polymeric nanoparticles, including AgNPs and AuNPs, are also used as anti-infective and anti-inflammatory agents in primary therapeutic mediators. Numerous reports have shown that healthcare professionals use AgNPs and AuNPs to deliver unconditional and controlled drug delivery. Furthermore, those NPs act as anti-infective and antibiotics against bacterial infections. Thus, hospitals require these NPs for diabetic wound healing [140]. As a result, AgNPs have a much greater effect on wound healing than APS. It has also been noted that Au alone cannot perform any biological activity such as anti-microbial activity. It must be bound or combined with some biomolecules to show activity against damaged tissue/regeneration activity [141]. AuNPs coated with peptides and enzymes lead to faster healing of diabetic wounds in an animal model [142]. In another study, wound healing was nearly 80%, and the injury site was closed within six days with KGF coated AuNPs in diabetic rat model [143].

In general, overexpression of GM3S causes slow wound healing due to the high insulin levels and resistance. This was demonstrated in a mice mode. The treatment with Au-NPs combined with peptide LL37 and plasmid DNA showed better histopathological effects on the injury site and reduced pathogenesis. As a result, Ag exhibits greater activity and functions when compared to Au. However, an *in vivo* study found that AgNPs with nanopolymers appear late in wound healing and may be reduced by a saline wash in the wound site. Furthermore, a delayed

Table 3
Some of the important Gene therapy method employed in the clinical management of DM.

Gene therapy	Model	Mode of action	Ref.
AAT	NOD mouse	Modifies the T cell receptor repertoire, Reduces cell-mediated autoimmunity	[123]
NeuroD/BETA2	NOD mouse	Reverse the hyperglycemia, induce islet neogenesis	[124]
rAAA-insulin analog	Sprague–Dawley rats	Cure the autoimmune-mediated diabetes, Reduction of type 1 diabetes	[125]
OGT2115	C57BL/6J mice	Aggravates hyperglycemia, Stimulates the infiltration of immunocytes	[126]
ADi-100	diabetic mice	Reversing the hyperglycemia improved the apoptosis stimulating Bax content	[127]
GAD65206-220 GAD65536-550, Insulin B9-23 and Insulin C17-A1	Nude mice	Induce the IL-10 and TGF-β expression in pTregs, silencing the autoreactive T cells, Modulates DCs by upregulating Il-10^{hi} and downregulating CD40^{lo}	[128]
Klotho	db/db mouse	Decrease the blood glucose, Improve the hormonal effect in autocrine and paracrine effects	[129]
DsAAV8–MIP–GLP-1	Male-balb/c mice	Reduce autoimmune destruction including beta-cell expression of interleukin-4, mitigate the onset of diabetes	[130]
AAV2/8-	C57BL/6 male mice	Trigger capsid specific CD8^{+} T cell responses, Promoted the environment less immunologically tolerant	[131]
LentiVIP	Sprague Dawley rats	Reverses hyperglycemia, prevents weight loss normally, suppression of Th1 cytokines, activation of regulatory T cells, and increased IL-10 synthesis	[132]
FGF21	High fat diet-induced diabetic rat	Favor the weight loss, Reduced the inflammation and fat accumulation in adipose tissue; reverse the steatosis and fibrosis, increase the insulin sensitivity, decrease the risk of tumor formation due to HFD	[133]

inhibition of the bacterial cell wall resulted in an irreversible stop. Zinc is another trace element used to treat both T1 and T2 DM in the form of ZnO and ZnO_2 NPPs. Zinc is an essential co-factor that promotes metabolic homeostasis by accelerating the activity of over 300 enzymes and co-enzymes during metabolism. In general, Zn is used to maintain or lower hypertension and high blood glucose levels by absorbing glucose and storing it in skeletal and adipose tissue as glycogen. With this metabolic activity, Zn is being studied as ZnO NPs for therapeutic applications, biomedicine engineering, pharmaceutical industries, andrology applications and finally used as a local nutrient for hair treatment [144]. Since the bioavailability of ZnO is high and first-pass metabolism is maximum, it will be a better candidate than other NPs. Also, the ZnO has been studied against melanoma, inflammation, bacterial infection and diabetes. They have also been effective in healing chronic diabetic wounds and injuries [145]. ZnO NPs with polymeric gel combined biomolecules have been experimented against diabetic induced Sprague-Dawley rats. Ceramic nanoparticles are used as a transporter to deliver the drug to the target site of injury or inflammatory site. Hence, these ceramic NPs act as shuttle to deliver the drugs [146].

10. Conclusion

Diabetes mellitus is a metabolic disorder caused by the absence or low secretion of insulin with uncontrolled glucose elevation in the blood. Genetic inheritance, uncontrolled diet, sleep apnea, obesity, lifestyle, and occupational factors play a significant role in developing diabetes. Also, it is not a gender or age-based one. Hormonal therapy, allopathy, natural plant-mediated or green/chemical-mediated nanoparticle drug delivery, and various gene therapy methods are followed to control or manage blood glucose levels well. There are numerous management options for diabetic wound therapy now available. Traditional approaches have several drawbacks. One of the key constraints of traditional diabetic wound management therapy is the rate and progression of healing of a diabetic wound. Several nanotechnologies and nanoproducts have recently entered the market, showing promising results for diabetic wounds.

CRediT authorship contribution statement

Arokia Vijaya Anand Mariadoss: Conceptualization, Methodology, Validation, Data curation, Writing – original draft. **Allur Subramaniyan Sivakumar:** Validation, Data curation, Writing – review & editing. **Chang-Hun Lee:** Visualization, Writing – review & editing. **Sung Jae Kim**: Funding acquisition, Project administration, Supervision. Writing – review & editing. All authors gave final approval of the published article and are accountable for all aspects of the work.

Data Availability

The data presented in this study are available on request.

Conflict of interest

All authors have no conflicts of interests to be declared.

Data availability

Data will be made available on request.

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References

[1] Ramachandran, C. Snehalatha, A. Nanditha, Classification and diagnosis of diabetes, Textb. Diabetes (2017) 23–28.
[2] L.M. Thorn, C. Forsblom, J. Wadén, M. Saraheimo, N. Tolonen, K. Hietala, P.-H. Groop, F.D.N.S. Group, Metabolic syndrome as a risk factor for cardiovascular

disease, mortality, and progression of diabetic nephropathy in type 1 diabetes, Diabetes Care 32 (5) (2009) 950–952.
[3] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (1) (2010) 4–14.
[4] M. Hod, A. Kapur, D.A. Sacks, E. Hadar, M. Agarwal, G.C. Di Renzo, L.C. Roura, H.D. McIntyre, J.L. Morris, H. Divakar, The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care, Int. J. Gynecol. Obstet. 131 (2015) S173–S211.
[5] K. Tamarai, J.S. Bhatti, P.H. Reddy, Molecular and cellular bases of diabetes: focus on type 2 diabetes mouse model-TallyHo, Biochim. Biophys. Acta (BBA)-Mol. Basis Dis. 1865 (9) (2019) 2276–2284.
[6] J. Ilonen, J. Lempainen, R. Veijola, The heterogeneous pathogenesis of type 1 diabetes mellitus, Nat. Rev. Endocrinol. 15 (11) (2019) 635–650.
[7] A. Marin-Guerrero, J. Gutierrez-Fisac, P. Guallar-Castillon, J. Banegas, F. Rodríguez-Artalejo, Eating behaviours and obesity in the adult population of Spain, Br. J. Nutr. 100 (5) (2008) 1142–1148.
[8] C.V. Senaratna, J.L. Perret, C.J. Lodge, A.J. Lowe, B.E. Campbell, M.C. Matheson, G.S. Hamilton, S.C. Dharmage, Prevalence of obstructive sleep apnea in the general population: a systematic review, Sleep Med. Rev. 34 (2017) 70–81.
[9] A. Fagot-Campagna, Emergence of type 2 diabetes mellitus in children: epidemiological evidence: division of diabetes translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, J. Pediatr. Endocrinol. Metab. 13 (Suppl.) (2000) S1395–S1402.
[10] D.O. Baliunas, B.J. Taylor, H. Irving, M. Roerecke, J. Patra, S. Mohapatra, J. Rehm, Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis, Diabetes Care 32 (11) (2009) 2123–2132.
[11] J.E. Sprague, A.M. Arbeláez, Glucose counterregulatory responses to hypoglycemia, Pediatr. Endocrinol. Rev. 9 (1) (2011) 463–475.
[12] J.E. Campbell, C.B. Newgard, Mechanisms controlling pancreatic islet cell function in insulin secretion, Nat. Rev. Mol. Cell Biol. 22 (2) (2021) 142–158.
[13] E. Gendaszewska-Darmach, M.A. Garstka, K.M. Błażewska, Targeting small GTPases and their prenylation in diabetes mellitus, J. Med. Chem. 64 (14) (2021) 9677–9710.
[14] X. Huang, G. Liu, J. Guo, Z. Su, The PI3K/AKT pathway in obesity and type 2 diabetes, Int. J. Biol. Sci. 14 (11) (2018) 1483–1496.
[15] J. Rojas, V. Bermudez, J. Palmar, M.S. Martínez, L.C. Olivar, M. Nava, D. Tomey, M. Rojas, J. Salazar, C. Garicano, M. Velasco, Pancreatic beta cell death: novel potential mechanisms in diabetes therapy, J. Diabetes Res. 2018 (2018), 9601801.
[16] A.S. Sivakumar, P. Viswanathan, C.V. Anuradha, Dose-dependent effect of galangin on fructose-mediated insulin resistance and oxidative events in rat kidney, Front. Endocrinol. 15 (5) (2010) 224–232.
[17] M. Bodmer, C. Meier, S. Krähenbühl, S.S. Jick, C.R. Meier, Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis, Diabetes Care 31 (11) (2008) 2086–2091.
[18] M. Nauck, Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, Diabetes Obes. Metab. 18 (3) (2016) 203–216.
[19] M. Ekor, The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety, Front. Pharm. 4 (2014) (177-177).
[20] D.R. Lobos, I.A. Vicuña, V. Novik, C.A. Vega, Effect of high and low glycemic index breakfast on postprandial metabolic parameters and satiety in subjects with type 2 diabetes mellitus under intensive insulin therapy: controlled clinical trial, Clin. Nutr. ESPEN 20 (2017) 12–16.
[21] J.J. Mendes, J. Neves, Diabetic foot infections: current diagnosis and treatment, J. Diabet. Foot Complicat. (2012) 26–45.
[22] R.G. Frykberg, P.J. Franks, M. Edmonds, J.N. Brantley, L. Téot, T. Wild, M. G. Garoufalis, A.M. Lee, J.A. Thompson, G. Reach, A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study, Diabetes Care 43 (3) (2020) 616–624.
[23] Q. Gong, P. Zhang, J. Wang, J. Ma, Y. An, Y. Chen, B. Zhang, X. Feng, H. Li, X. Chen, Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study, Lancet Diabetes Endocrinol. 7 (6) (2019) 452–461.
[24] K.E. Chatwin, C.A. Abbott, A.J.M. Boulton, F.L. Bowling, N.D. Reeves, The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration–a comprehensive review, Diabetes/Metab. Res. Rev. 36 (4) (2020), e3258.
[25] S. Kehlenbrink, J. Smith, É. Ansbro, D.C. Fuhr, A. Cheung, R. Ratnayake, P. Boulle, K. Jobanputra, P. Perel, B. Roberts, The burden of diabetes and use of diabetes care in humanitarian crises in low-income and middle-income countries, Lancet Diabetes Endocrinol. 7 (8) (2019) 638–647.
[26] P. Hanlon, I. Fauré, N. Corcoran, E. Butterly, J. Lewsey, D. McAllister, F.S. Mair, Frailty measurement, prevalence, incidence, and clinical implications in people with diabetes: a systematic review and study-level meta-analysis, Lancet Healthy Longev. 1 (3) (2020) e106–e116.
[27] T. Riandini, D. Pang, M.P.H.S. Toh, C.S. Tan, D.Y.K. Liu, A.M.T.L. Choong, S. Chandrasekar, E.S. Tai, K.B. Tan, K. Venkataraman, Diabetes-related lower extremity complications in a multi-ethnic Asian population: a 10 year observational study in Singapore, Diabetologia 64 (7) (2021) 1538–1549.
[28] Y. Ezzatvar, R. Ramírez-Vélez, M. Izquierdo, A. García-Hermoso, Racial differences in all-cause mortality and future complications among people with diabetes: a systematic review and meta-analysis of data from more than 2.4 million individuals, Diabetologia 64 (11) (2021) 2389–2401.
[29] K. Ousey, P. Chadwick, A. Jawień, G. Tariq, H.K.R. Nair, J.L. Lázaro-Martínez, K. Sandy-Hodgetts, P. Alves, S. Wu, Z. Moore, Identifying and treating foot ulcers in patients with diabetes: saving feet, legs and lives, J. Wound Care 27 (Suppl. 5) (2018) S1–S52.
[30] A. Alavi, R.G. Sibbald, D. Mayer, L. Goodman, M. Botros, D.G. Armstrong, K. Woo, T. Boeni, E.A. Ayello, R.S. Kirsner, Diabetic foot ulcers: Part I. Pathophysiology and prevention, J. Am. Acad. Dermatol. 70 (1) (2014) 1–e1.
[31] F.W. Wagner Jr., The dysvascular foot: a system for diagnosis and treatment, Foot Ankle 2 (2) (1981) 64–122.
[32] B.A. Lipsky, A.R. Berendt, H.G. Deery, J.M. Embil, W.S. Joseph, A.W. Karchmer, J.L. LeFrock, D.P. Lew, J.T. Mader, C.J. Norden, J.S. Tan, Infectious Diseases Society of America, Diagnosis and treatment of diabetic foot infections, Plast. Reconstr. Surg. 117 (Sup 7) (2006) 212S–238S.
[33] A.K.C. Jain, S. Joshi, Diabetic foot classifications: review of literature, Med. Sci. 2 (3) (2013) 715–721.
[34] L. Corum, Ulcer and wound care: getting to the depth of the tissue, Natl. Cent. Contin. Educ. (2019).
[35] L. Chethan, K.M. Amith, Clinicopathological study and management of diabetic foot, Int. Surg. J. 4 (12) (2017) 3928–3932.
[36] A. Hingorani, G.M. LaMuraglia, P. Henke, M.H. Meissner, L. Loretz, K.M. Zinszer, V.R. Driver, R. Frykberg, T.L. Carman, W. Marston, The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine, J. Vasc. Surg. 63 (2) (2016) 3S–21S.
[37] D.A. Oni, Foot Self-Care Practices among Patients with Type 2 Diabetes and Diabetic Foot Ulcers: The Lived Experience, Washington State University, 2018.
[38] A. Tallis, T.A. Motley, R.P. Wunderlich, J.E. Dickerson Jr., C. Waycaster, H. B. Slade, G. Collagenase Diabetic Foot Ulcer Study, Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study, Clin. Ther. 35 (11) (2013) 1805–1820.
[39] J.A. Witkowski, L.C. Parish, Debridement of cutaneous ulcers: medical and surgical aspects, Clin. Dermatol. 9 (4) (1991) 585–591.
[40] S. Shah, G. Abbas, M. Hanif, Anees-Ur-Rehman, M. Zaman, N. Riaz, A. Altaf, S. U. Hassan, U. Saleem, A. Shah, Increased burden of disease and role of health economics: Asia-pacific region, Expert Rev. Pharm. Outcomes Res. 19 (5) (2019) 517–528.
[41] T.A. Schwetz, C.A. Reissaus, D.W. Piston, Differential stimulation of insulin secretion by GLP-1 and Kisspeptin-10, PLoS One 9 (11) (2014), e113020.
[42] M. Lipsett, S. Hanley, M. Castellarin, E. Austin, W.L. Suarez-Pinzon, A. Rabinovitch, L. Rosenberg, The role of islet neogenesis-associated protein (INGAP) in islet neogenesis, Cell Biochem. Biophys. 48 (2) (2007) 127–137.
[43] C.E. Quinn, P.K. Hamilton, C.J. Lockhart, G.E. McVeigh, Thiazolidinediones: effects on insulin resistance and the cardiovascular system, Br. J. Pharm. 153 (4) (2008) 636–645.
[44] D. Sola, L. Rossi, G.P.C. Schianca, P. Maffioli, M. Bigliocca, R. Mella, F. Corlianò, G.P. Fra, E. Bartoli, G. Derosa, Sulfonylureas and their use in clinical practice, Arch. Med. Sci. 11 (4) (2015) 840–848.
[45] C.M. Apovian, J. Okemah, P.M. O'Neil, Body weight considerations in the management of Type 2 diabetes, Adv. Ther. 36 (1) (2019) 44–58.
[46] R. Murali, S. Srinivasan, N. Ashokkumar, Antihyperglycemic effect of fraxetin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats, Biochimie 95 (10) (2013) 1848–1854.
[47] R. Vinayagam, B. Xu, Anti-diabetic properties of dietary flavonoids: a cellular mechanism review, Nutr. Metab. 12 (1) (2015) 60.
[48] S. Srinivasan, L. Pari, Ameliorative effect of diosmin, a citrus flavonoid against streptozotocin-nicotinamide generated oxidative stress induced diabetic rats, Chem.-Biol. Interact. 195 (1) (2012) 43–51.
[49] S. Srinivasan, V. Vinothkumar, R. Murali, Chapter 22 – anti-diabetic efficacy of citrus fruits with special allusion to flavone glycosides, in: R.R. Watson, V. R. Preedy (Eds.), Bioactive Food as Dietary Interventions for Diabetes, Second edition, Academic Press, 2019, pp. 335–346.
[50] S. Dewanjee, P. Chakraborty, B. Mukherjee, V. De Feo, Plant-based antidiabetic nanoformulations: the emerging paradigm for effective therapy, Int. J. Mol. Sci. 21 (6) (2020) 2217.
[51] K.J. Cash, H.A. Clark, Nanosensors and nanomaterials for monitoring glucose in diabetes, Trends Mol. Med. 16 (12) (2010) 584–593.
[52] M.N. Singh, K.S.Y. Hemant, M. Ram, H.G. Shivakumar, Microencapsulation: a promising technique for controlled drug delivery, Res. Pharm. Sci. 5 (2) (2010) 65–77.
[53] J. De Souza Rebouças, I. Esparza, M. Ferrer, M.L. Sanz, J.M. Irache, C. Gamazo, Nanoparticulate adjuvants and delivery systems for allergen immunotherapy, J. Biomed. Biotechnol. 2012 (2012) (474605-474605).
[54] W.H. De Jong, P.J.A. Borm, Drug delivery and nanoparticles: applications and hazards, Int. J. Nanomed. 3 (2) (2008) 133–149.
[55] A.V.A. Mariadoss, R. Vinyagam, V. Rajamanickam, V. Sankaran, S. Venkatesan, E. David, Pharmacological aspects and potential use of phloretin: a systemic review, Mini Rev. Med. Chem. 19 (13) (2019) 1060–1067.
[56] A.V.A. Mariadoss, R. Vinayagam, V. Senthilkumar, M. Paulpandi, K. Murugan, B. Xu, G. K.M, V.S. Kotakadi, E. David, Phloretin loaded chitosan nanoparticles augments the pH-dependent mitochondrial-mediated intrinsic apoptosis in human oral cancer cells, Int. J. Biol. Macromol. 130 (2019) 997–1008.
[57] J. Muthukumaran, S. Srinivasan, R.S. Venkatesan, V. Ramachandran, U. Muruganathan, Syringic acid, a novel natural phenolic acid, normalizes

hyperglycemia with special reference to glycoprotein components in experimental diabetic rats, J. Acute Dis. 2 (4) (2013) 304–309.
[58] S. Vijayakumar, R. Vinayagam, M.A.V. Anand, K. Venkatachalam, K. Saravanakumar, M.-H. Wang, S. Casimeer C, G. Km, E. David, Green synthesis of gold nanoparticle using Eclipta alba and its anti-diabetic activities through regulation of Bcl-2 expression in pancreatic cell line, J. Drug Deliv. Sci. Technol. 58 (2020), 101786.
[59] V. Ramachandran, M. Arokia Vijaya Anand, E. David, K. Venkatachalam, S. Vijayakumar, V. Sankaran, A. Balupillai, C.C. Sangeetha, K.M. Gothandam, V. S. Kotakadi, A. Ghidan, T. Al Antary, B. Xu, Anti-diabetic activity of gold nanoparticles synthesized using wedelolactone in RIN-5F cell line, Antioxidants 9 (1) (2020) 8.
[60] A.V.A. Mariadoss, S. Park, K. Saravanakumar, A. Sathiyaseelan, M.-H. Wang, Ethyl acetate fraction of Helianthus tuberosus L. induces anti-diabetic, and wound-healing activities in insulin-resistant human liver cancer and mouse fibroblast cells, Antioxidants 10 (1) (2021) 99.
[61] A.S. Sivakumar, C.V. Anuradha, Effect of galangin supplementation on oxidative damage and inflammatory changes in fructose-fed rat liver, Chem.-Biol. Interact. 193 (2) (2011) 141–148.
[62] K. Saravanakumar, A. Sathiyaseelan, A.V.A. Mariadoss, M.-H. Wang, Antioxidant and anti-diabetic properties of biocompatible ceria oxide (CeO2) nanoparticles in mouse fibroblast NIH3T3 and insulin resistant HepG2 cells, Ceram. Int. 47 (6) (2021) 8618–8626.
[63] R. Vinayagam, J. Xiao, B. Xu, An insight into anti-diabetic properties of dietary phytochemicals, Phytochem. Rev. 16 (3) (2017) 535–553.
[64] U. Muruganathan, S. Srinivasan, D. Indumathi, Antihyperglycemic effect of carvone: effect on the levels of glycoprotein components in streptozotocin-induced diabetic rats, J. Acute Dis. 2 (4) (2013) 310–315.
[65] S.A. Amiel, Diabetic control and complications, BMJ 307 (6909) (1993) 881–882.
[66] X. Nie, Z. Chen, L. Pang, L. Wang, H. Jiang, Y. Chen, Z. Zhang, C. Fu, B. Ren, J. Zhang, Oral nano drug delivery systems for the treatment of type 2 diabetes mellitus: an available administration strategy for antidiabetic phytocompounds, Int. J. Nanomed. 15 (2020) 10215–10240.
[67] H. Ahn, J.-H. Park, Liposomal delivery systems for intestinal lymphatic drug transport, Biomater. Res. 20 (2016) (36-36).
[68] A.V.A. Mariadoss, R. Vinayagam, B. Xu, K. Venkatachalam, V. Sankaran, S. Vijayakumar, S.R. Bakthavatsalam, S.A. Mohamed, E. David, Phloretin loaded chitosan nanoparticles enhance the antioxidants and apoptotic mechanisms in DMBA induced experimental carcinogenesis, Chem.-Biol. Interact. 308 (2019) 11–19.
[69] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, Md.P. Rodriguez-Torres, L. S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H.-S. Shin, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (1) (2018) 71.
[70] K. Saravanakumar, X. Hu, S. Shanmugam, R. Chelliah, P. Sekar, D.-H. Oh, K. Kathiresan, M.-H. Wang, Enhanced cancer therapy with pH-dependent and aptamer functionalized doxorubicin loaded polymeric (poly D,L-lactic-co-glycolic acid) nanoparticles, Arch. Biochem. Biophys. 671 (2019).
[71] F. Yu, M. Ao, X. Zheng, N. Li, J. Xia, Y. Li, D. Li, Z. Hou, Z. Qi, X.D. Chen, PEG–lipid–PLGA hybrid nanoparticles loaded with berberine–phospholipid complex to facilitate the oral delivery efficiency, Drug Deliv. 24 (1) (2017) 825–833.
[72] E.B. Souto, S.B. Souto, J.R. Campos, P. Severino, T.N. Pashirova, L.Y. Zakharova, A.M. Silva, A. Durazzo, M. Lucarini, A.A. Izzo, A. Santini, Nanoparticle delivery systems in the treatment of diabetes complications, Molecules (2019).
[73] A. Pudlarz, J. Szemraj, Nanoparticles as carriers of proteins, peptides and other therapeutic molecules, Open Life Sci. 13 (1) (2018) 285–298.
[74] S. Fayyaz, D. Ahmed, S. Khalid, S.N. Khan, M.R. Shah, M.I. Choudhary, Synthesis of vildagliptin conjugated metal nanoparticles for type II diabetes control: targeting the DPP-IV enzyme, New J. Chem. 44 (47) (2020) 20853–20860.
[75] V. Ramachandran, M. Arokia Vijaya Anand, E. David, K. Venkatachalam, S. Vijayakumar, V. Sankaran, A. Balupillai, C.C. Sangeetha, K.M. Gothandam, V. S. Kotakadi, A. Ghidan, T. Al Antary, B. Xu, Anti-diabetic activity of gold nanoparticles synthesized using wedelolactone in RIN-5F cell line, Antioxidants 9 (1) (2020) 8.
[76] K. Balan, W. Qing, Y. Wang, X. Liu, T. Palvannan, Y. Wang, F. Ma, Y. Zhang, Anti-diabetic activity of silver nanoparticles from green synthesis using Lonicera japonica leaf extract, RSC Adv. 6 (46) (2016) 40162–40168.
[77] Y. Li, J. Zhang, J. Gu, S. Chen, Biosynthesis of polyphenol-stabilised nanoparticles and assessment of anti-diabetic activity, J. Photochem. Photobiol. B: Biol. 169 (2017) 96–100.
[78] D. Fan, L. Li, Z. Li, Y. Zhang, X. Ma, L. Wu, H. Zhang, F. Guo, Biosynthesis of selenium nanoparticles and their protective, antioxidative effects in streptozotocin induced diabetic rats, Sci. Technol. Adv. Mater. 21 (1) (2020) 505–514.
[79] A.K. Sharma, A. Kumar, G. Taneja, U. Nagaich, A. Deep, S.K. Rajput, Synthesis and preliminary therapeutic evaluation of copper nanoparticles against diabetes mellitus and -induced micro- (renal) and macro-vascular (vascular endothelial and cardiovascular) abnormalities in rats, RSC Adv. 6 (43) (2016) 36870–36880.
[80] S.-A. Chen, H.-M. Chen, Y.-D. Yao, C.-F. Hung, C.-S. Tu, Y.-J. Liang, Topical treatment with anti-oxidants and Au nanoparticles promote healing of diabetic wound through receptor for advance glycation end-products, Eur. J. Pharm. Sci. 47 (5) (2012) 875–883.
[81] N. Elassy, S. El-Dafrawy, A.O. Abd El-Azim, O.A.Y. El-Khawaga, A. Negm, Zinc oxide nanoparticles augment CD4, CD8, and GLUT-4 expression and restrict inflammation response in streptozotocin-induced diabetic rats, IET Nanobiotechnol. 14 (8) (2020) 680–687.
[82] G. Alomari, B. Al-Trad, S. Hamdan, A.A.A. Aljabali, M.S. Al Zoubi, K. Al-Batanyeh, J. Qar, G.J. Eaton, A.K. Alkaraki, W. Alshaer, S. Haifawi, K. Jemon, D. K. Chellappan, K. Dua, M.M. Tambuwala, Alleviation of diabetic nephropathy by zinc oxide nanoparticles in streptozotocin-induced type 1 diabetes in rats, IET Nanobiotechnol. 15 (5) (2021) 473–483.
[83] X. Li, M. Zhen, C. Zhou, R. Deng, T. Yu, Y. Wu, C. Shu, C. Wang, C. Bai, Gadofullerene nanoparticles reverse dysfunctions of pancreas and improve hepatic insulin resistance for type 2 diabetes mellitus treatment, ACS Nano 13 (8) (2019) 8597–8608.
[84] H.M. Aldawsari, A. Hanafy, G.S. Labib, J.M. Badr, Antihyperglycemic activities of extracts of the mistletoes Plicosepalus acaciae and P. curviflorus in comparison to their solid lipid nanoparticle suspension formulations, Zeitschrift fur Naturforschung. C, J. Biosci. 69 (9–10) (2014) 391–398.
[85] K. Priyanka, P.L. Sahu, S. Singh, Optimization of processing parameters for the development of Ficus religiosa L. extract loaded solid lipid nanoparticles using central composite design and evaluation of anti-diabetic efficacy, J. Drug Deliv. Sci. Technol. 43 (2018) 94–102.
[86] R. Panwar, N. Raghuwanshi, A.K. Srivastava, A.K. Sharma, V. Pruthi, In-vivo sustained release of nanoencapsulated ferulic acid and its impact in induced diabetes, Mater. Sci. Eng. C Mater. Biol. Appl. 92 (2018) 381–392.
[87] D. Chitkara, S.K. Nikalaje, A. Mittal, M. Chand, N. Kumar, Development of quercetin nanoformulation and in vivo evaluation using streptozotocin induced diabetic rat model, Drug Deliv. Transl. Res. 2 (2) (2012) 112–123.
[88] M.U. Akbar, K.M. Zia, M.S.H. Akash, A. Nazir, M. Zuber, M. Ibrahim, In-vivo anti-diabetic and wound healing potential of chitosan/alginate/maltodextrin/pluronic-based mixed polymeric micelles: curcumin therapeutic potential, Int. J. Biol. Macromol. 120 (2018) 2418–2430.
[89] A.K. Singh, H. Pandey, P.W. Ramteke, S.B. Mishra, Nano-suspension of ursolic acid for improving oral bioavailability and attenuation of type II diabetes: a histopathological investigation, Biocatal. Agric. Biotechnol. 22 (2019), 101433.
[90] Z. Wang, J. Wu, Q. Zhou, Y. Wang, T. Chen, Berberine nanosuspension enhances hypoglycemic efficacy on streptozotocin induced diabetic C57BL/6 mice, Evid. Based Complement. Altern. Med. 2015 (2015), 239749.
[91] K. Gourishetti, R. Keni, P.G. Nayak, S.R. Jitta, N.A. Bhaskaran, L. Kumar, N. Kumar, N. Krishnadas, R.R. Shenoy, Sesamol-loaded PLGA nanosuspension for accelerating wound healing in diabetic foot ulcer in rats, Int. J. Nanomed. 15 (2020) 9265–9282.
[92] P.K. Gaur, Nanosuspension of flavonoid-rich fraction from Psidium guajava Linn for improved type 2-diabetes potential, J. Drug Deliv. Sci. Technol. 62 (2021), 102358.
[93] S.B. Mishra, N. Kumari, Engineering of crystalline nano-suspension of lycopene for potential management of oxidative stress–linked diabetes in experimental animals, BioNanoScience 11 (2) (2021) 345–354.
[94] S.K. Yadav, S. Mishra, B. Mishra, Eudragit-based nanosuspension of poorly water-soluble drug: formulation and in vitro-in vivo evaluation, AAPS PharmSciTech 13 (4) (2012) 1031–1044.
[95] V. Piazzini, L. Micheli, C. Luceri, M. D'Ambrosio, L. Cinci, C. Ghelardini, A. R. Bilia, L. Di Cesare Mannelli, M.C. Bergonzi, Nanostructured lipid carriers for oral delivery of silymarin: improving its absorption and in vivo efficacy in type 2 diabetes and metabolic syndrome model, Int. J. Pharm. 572 (2019), 118838.
[96] J. Natarajan, B.K.R. Sanapalli, M. Bano, S.K. Singh, M. Gulati, V.V.S.R. Karri, Nanostructured lipid carriers of pioglitazone loaded collagen/chitosan composite Scaffold for diabetic wound healing, Adv. Wound Care 8 (10) (2019) 499–513.
[97] H.-J. Lee, M. Jeong, Y.-G. Na, S.-J. Kim, H.-K. Lee, C.-W. Cho, An EGF- and curcumin-co-encapsulated nanostructured lipid carrier accelerates chronic-wound healing in diabetic rats, Molecules 25 (20) (2020) 4610.
[98] A. Motawea, A.E.-G.H. Abd El-Gawad, T. Borg, M. Motawea, M. Tarshoby, The impact of topical phenytoin loaded nanostructured lipid carriers in diabetic foot ulceration, Foot 40 (2019) 14–21.
[99] F. Shi, Z. Wei, Y. Zhao, X. Xu, Nanostructured lipid carriers loaded with baicalin: an efficient carrier for enhanced anti-diabetic effects, Pharmacogn. Mag. 12 (47) (2016) 198–202.
[100] H.R. Alexander, S.S. Syed Alwi, L.S. Yazan, F.H. Zakarial Ansar, Y.S. Ong, Migration and proliferation effects of thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) and thymoquinone (TQ) on in vitro wound healing models, Evid.-Based Complement. Altern. Med. 2019 (2019), 9725738.
[101] P. Sharma, P. Saxena, A. Jaswanth, M. Chalamaiah, A. Balasubramaniam, Anti-diabetic activity of lycopene niosomes: experimental observation, J. Pharm. Drug Dev. 4 (2017) 103.
[102] H.Y. Xu, C.S. Liu, C.L. Huang, L. Chen, Y.R. Zheng, S.H. Huang, X.Y. Long, Nanoemulsion improves hypoglycemic efficacy of berberine by overcoming its gastrointestinal challenge, Colloids Surf. B Biointerfaces 181 (2019) 927–934.
[103] M.S. Alam, A. Ahad, L. Abidin, M. Aqil, S.R. Mir, M. Mujeeb, Embelin-loaded oral niosomes ameliorate streptozotocin-induced diabetes in Wistar rats, Biomed. Pharmacother. 97 (2018) 1514–1520.
[104] M. Haider, J. Kanoujia, c.b. Tripathi, M. Arya, G. Kaithwas, S. Saraf, Pioglitazone loaded vesicular carriers for anti-diabetic activity: development and optimization as per central composite design, J. Pharm. Sci. Pharmacol. 2 (1) (2015) 11–20.
[105] Kamble, S. Talreja, A. Gupta, D. Patil, D. Pathak, I. Moothedath, B. Duraiswamy, Development and biological evaluation of Gymnema sylvestre extract-loaded nonionic surfactant-based niosomes, Nanomedicine 8 (8) (2013) 1295–1305.
[106] K.M. Raafat, S.A. El-Zahaby, Niosomes of active Fumaria officinalis phytochemicals: anti-diabetic, antineuropathic, anti-inflammatory, and possible mechanisms of action, Chin. Med. 15 (1) (2020) 40.

[107] J. Zhang, J. Zhou, T. Zhang, Z. Niu, J. Wang, J. Guo, Z. Li, Z. Zhang, Facile fabrication of an amentoflavone-loaded micelle system for oral delivery to improve bioavailability and hypoglycemic effects in KKAy mice, ACS Appl. Mater. Interfaces 11 (13) (2019) 12904–12913.
[108] Y.M. El-Far, M.M. Zakaria, M.M. Gabr, A.M. El Gayar, I.M. El-Sherbiny, L.A. Eissa, A newly developed silymarin nanoformulation as a potential anti-diabetic agent in experimental diabetes, Nanomedicine 11 (19) (2016) 2581–2602.
[109] S. Amjadi, M. Mesgari Abbasi, B. Shokouhi, M. Ghorbani, H. Hamishehkar, Enhancement of therapeutic efficacy of betanin for diabetes treatment by liposomal nanocarriers, J. Funct. Foods 59 (2019) 119–128.
[110] E.G. Spanakis, F. Chiarugi, A. Kouroubali, S. Spat, P. Beck, S. Asanin, P. Rosengren, T. Gergely, J. Thestrup, Diabetes management using modern information and communication technologies and new care models, Interact. J. Med. Res. 1 (2) (2012) (e8-e8).
[111] Bruen, C. Delaney, L. Florea, D. Diamond, Glucose sensing for diabetes monitoring: recent developments, Sensors 17 (8) (2017) 1866.
[112] B.L. Wajchenberg, Beta-cell failure in diabetes and preservation by clinical treatment, Endocr. Rev. 28 (2) (2007) 187–218.
[113] J. Størling, F. Pociot, Type 1 diabetes candidate genes linked to pancreatic islet cell inflammation and beta-cell apoptosis, Genes 8 (2) (2017) 72.
[114] M.S. Wong, W.J. Hawthorne, N. Manolios, Gene therapy in diabetes, Self Nonself 1 (3) (2010) 165–175.
[115] B.O. Roep, S. Thomaidou, R. van Tienhoven, A. Zaldumbide, Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?), Nat. Rev. Endocrinol. 17 (3) (2021) 150–161.
[116] M.A. Coleman, C.F. Jessup, J.A. Bridge, N.H Overgaard, D. Penko, S. Walters, D. J. Borg, R. Galea, J.M. Forbes, R. Thomas, P.T.C. Coates, S.T. Grey, J.W. Wells, R. J. Steptoe, Antigen-encoding bone marrow terminates islet-directed memory CD8 $^{+}$ T-cell responses to alleviate islet transplant rejection, Diabetes 65 (5) (2016) 1328–1340.
[117] S. Song, C. Wasserfall, Y.C. Zhang, M. Kapturczak, A. Muir, M. Powers, M. Scott-Jorgensen, M. Campbell-Thompson, J.M. Crawford, T.M. Ellis, T.R. Flotte, M. A Atkinson, Adeno-associated virus vector-mediated IL-10 gene delivery prevents type 1 diabetes in NOD mice, Proc. Natl. Acad. Sci. USA 98 (24) (2001) 13913–13918.
[118] Z. Fu, E.R. Gilbert, D. Liu, Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes, Curr. Diabetes Rep. 9 (1) (2013) 25–53.
[119] J. Han, B. McLane, E.-H. Kim, J.-W. Yoon, H.-S. Jun, Remission of diabetes by insulin gene therapy using a hepatocyte-specific and glucose-responsive synthetic promoter, Mol. Ther. 19 (3) (2011) 470–478.
[120] A.I. Romer, L. Sussel, Pancreatic islet cell development and regeneration, Curr. Opin. Endocrinol. Diabetes Obes. 22 (4) (2015) 255–264.
[121] P.M. Thulé, A.G. Campbell, D. Jia, Y. Lin, S. You, S. Paveglio, D.E. Olson, M. Kozlowski, Long-term glycemic control with hepatic insulin gene therapy in streptozotocin-diabetic mice, J. Gene Med. 17 (8–9) (2015) 141–152.
[122] A. Binda, C. Murano, I. Rivolta, Innovative therapies and nanomedicine applications for the treatment of Alzheimer's disease: a state-of-the-art (2017–2020), Int. J. Nanomed. 15 (2020) 6113–6135.
[123] Y. Lu, M. Tang, C. Wasserfall, Z. Kou, M. Campbell-Thompson, T. Gardemann, J. Crawford, M. Atkinson, S. Song, α 1-antitrypsin gene therapy modulates cellular immunity and efficiently prevents type 1 diabetes in nonobese diabetic mice, Hum. Gene Ther. 17 (6) (2006) 625–634.
[124] H. Kojima, M. Fujimiya, K. Matsumura, P. Younan, H. Imaeda, M. Maeda, L. Chan, NeuroD-betacellulin gene therapy induces islet neogenesis in the liver and reverses diabetes in mice, Nat. Med. 9 (5) (2003) 596–603.
[125] H.C. Lee, S.-J. Kim, K.-S. Kim, H.-C. Shin, J.-W. Yoon, Remission in models of type 1 diabetes by gene therapy using a single-chain insulin analogue, Nature 408 (6811) (2000) 483–488.
[126] W.-Y. Song, X.-H. Jiang, Y. Ding, Y. Wang, M.-X. Zhou, Y. Xia, C.-Y. Zhang, C.-C. Yin, C. Qiu, K. Li, P. Sun, X. Han, Inhibition of heparanase protects against pancreatic beta cell death in streptozotocin-induced diabetic mice via reducing intra-islet inflammatory cell infiltration, Br. J. Pharm. 177 (19) (2020) 4433–4447.
[127] Alleva, M. Rezaee, L. Yip, G. Ren, J. Rosenberg, W. Concepcion, A. Escher, S. Shabahang, A. Thakor, Reversal of hyperglycemia and suppression of type 1 diabetes in the NOD mouse with apoptotic DNA immunotherapyTM (ADiTM), ADi-100, Biomedicines 8 (2020) 53.
[128] X. Zhou, S. Zhang, F. Yu, G. Zhao, S. Geng, W. Yu, X.-Y. Wang, B. Wang, Tolerogenic vaccine composited with islet-derived multipeptides and cyclosporin A induces pTreg and prevents Type 1 diabetes in murine model, Hum. Vaccin. Immunother. 16 (2) (2020) 240–250.
[129] E.A. Forsberg, H. Olauson, T. Larsson, S.B. Catrina, Effect of systemically increasing human full-length Klotho on glucose metabolism in db/db mice, Diabetes Res. Clin. Pract. 113 (2016) 208–210.
[130] M.J. Riedel, D.F. Gaddy, A. Asadi, P.D. Robbins, T.J. Kieffer, DsAAV8-mediated expression of glucagon-like peptide-1 in pancreatic beta-cells ameliorates streptozotocin-induced diabetes, Gene Ther. 17 (2) (2010) 171–180.
[131] A. Recino, S.U. Gan, K.C. Sia, Y. Sawyer, J. Trendell, R. Kay, F.M. Gribble, F. Reimann, R. Foale, M. Notaridou, N. Holmes, A. Lever, K.O. Lee, A. Nathwani, A. Cooke, R. Calne, M. Wallberg, Immunosuppression overcomes insulin- and vector-specific immune responses that limit efficacy of AAV2/8-mediated insulin gene therapy in NOD mice, Gene Ther. 26 (1) (2019) 40–56.
[132] Erendor, E.O. Sahin, A.D. Sanlioglu, M.K Balci, T.S. Griffith, S. Sanlioglu, Lentiviral gene therapy vectors encoding VIP suppressed diabetes-related inflammation and augmented pancreatic beta-cell proliferation, Gene Ther. 28 (2020) 130–141.
[133] V. Jimenez, C. Jambrina, E. Casana, V. Sacristan, S. Muñoz, S. Darriba, J. Rodó, C. Mallol, M. Garcia, X. León, S. Marcó, A. Ribera, I. Elias, A. Casellas, I. Grass, G. Elias, T. Ferré, S. Motas, S. Franckhauser, F. Mulero, M. Navarro, V. Haurigot, J. Ruberte, F. Bosch, FGF21 gene therapy as treatment for obesity and insulin resistance, EMBO Mol. Med. 10 (8) (2018), e8791.
[134] K. Ogurtsova, J.D. da Rocha Fernandes, Y. Huang, U. Linnenkamp, L. Guariguata, N.H. Cho, D. Cavan, J.E. Shaw, L.E. Makaroff, IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040, Diabetes Res. Clin. Pract. 128 (2017) 40–50.
[135] Dabiri, E. Damstetter, T. Phillips, Choosing a wound dressing based on common wound characteristics, Adv. Wound Care 5 (1) (2016) 32–41.
[136] K.R. Anilakumar, Technological advances in nano-science for specific food and nutrition delivery, Adv. Process. Technol. (2021) 97–121.
[137] M.M. Mihai, M.B. Dima, B. Dima, A.M. Holban, Nanomaterials for wound healing and infection control, Materials 12 (13) (2019) 2176.
[138] M. Parani, G. Lokhande, A. Singh, A.K. Gaharwar, Engineered nanomaterials for infection control and healing acute and chronic wounds, ACS Appl. Mater. Interfaces 8 (16) (2016) 10049–10069.
[139] W. Qiu, H. Han, M. Li, N. Li, Q. Wang, X. Qin, X. Wang, J. Yu, Y. Li, F. Li, Nanofibers reinforced injectable hydrogel with self-healing, antibacterial, and hemostatic properties for chronic wound healing, J. Colloid Interface Sci. 596 (2021) 312–323.
[140] S. Amin Yavari, S.M. Castenmiller, J.A.G. van Strijp, M. Croes, Combating implant infections: shifting focus from bacteria to host, Adv. Mater. 32 (43) (2020), 2002962.
[141] K. Varaprasad, Y.M. Mohan, S. Ravindra, N.N. Reddy, K. Vimala, K. Monika, B. Sreedhar, K.M. Raju, Hydrogel–silver nanoparticle composites: a new generation of anti-microbials, J. Appl. Polym. Sci. 115 (2) (2010) 1199–1207.
[142] R.K. Thapa, D.B. Diep, H.H. Tønnesen, Topical anti-microbial peptide formulations for wound healing: current developments and future prospects, Acta Biomater. 103 (2020) 52–67.
[143] S. Li, Q. Tang, H. Xu, Q. Huang, Z. Wen, Y. Liu, C. Peng, Improved stability of KGF by conjugation with gold nanoparticles for diabetic wound therapy, Nanomedicine 14 (22) (2019) 2909–2923.
[144] R.D. Umrani, K.M. Paknikar, Zinc oxide nanoparticles show anti-diabetic activity in streptozotocin-induced Type 1 and 2 diabetic rats, Nanomedicine 9 (1) (2014) 89–104.
[145] M.S. Saddik, M.M.A. Elsayed, M.A. El-Mokhtar, H. Sedky, J.A. Abdel-Aleem, A. M. Abu-Dief, M.F. Al-Hakkani, H.L. Hussein, S.A. Al-Shelkamy, F.Y. Meligy, A. Khames, H.A. Abou-Taleb, Tailoring of novel azithromycin-loaded zinc oxide nanoparticles for wound healing, Pharmaceutics 14 (1) (2022) 111.
[146] S.M. Mousavi, G. Behbudi, A. Gholami, S.A. Hashemi, Z.M. Nejad, S. Bahrani, W.-H. Chiang, L.C. Wei, N. Omidifar, Shape-controlled synthesis of zinc nanostructures mediating macromolecules for biomedical applications, Biomater. Res. 26 (1) (2022) 4.