



# Molecular prospect of type-2 diabetes: Nanotechnology based diagnostics and therapeutic intervention

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## Abstract

About ninety percent of all diabetic conditions account for T2D caused due to abnormal insulin secretion/ action or increased hepatic glucose production. Factors that contribute towards the aetiology of T2D could be well explained through biochemical, molecular, and cellular aspects. In this review, we attempt to explain the recent evolving molecular and cellular advancement associated with T2D pathophysiology. Current progress fabricated in T2D research concerning intracellular signaling cascade, inflammasome, autophagy, genetic and epigenetics changes is discretely explained in simple terms. Present available anti-diabetic therapeutic strategies commercialized and their limitations which are needed to be acknowledged are addressed in the current review. In particular, the pre-eminence of nanotechnology-based approaches to nullify the inadequacy of conventional anti-diabetic therapeutics and heterogeneous nanoparticulated systems exploited in diabetic researches are also discretely mentioned and are also listed in a tabular format in the review. Additionally, as a future prospect of nanotechnology, the review presents several strategic hypotheses to ameliorate the austerity of T2D by an engineered smart targeted nano-delivery system. In detail, an effort has been made to hypothesize novel nanotechnological based therapeutic strategies, which exploits previously described inflammasome, autophagic target points. Utilizing graphical description it is explained how a smart targeted nano-delivery system could promote  $\beta$ -cell growth and development by inducing the Wnt signaling pathway (inhibiting Gsk3 $\beta$ ), inhibiting inflammasome (inhibiting NLRP3), and activating autophagic target points (protecting Atg3/Atg7 complex from oxidative stress) thereby might ameliorate the severity of T2D. Additionally, several targeting molecules associated with autophagic and epigenetic factors are also highlighted, which can be exploited in future diabetic research.

**Keywords** Type-2 diabetes · Intracellular signaling cascade · Inflammasome · Autophagy · Epigenetics · Nano-delivery systems

## Major Objectives

- Cellular and molecular pathophysiology of T2D
- Commercialized antidiabetic drugs and their limitations
- Types of nanoparticulated systems exploited in diabetic researches
- Emerging intracellular signaling cascade that includes inflammasome, autophagy, genetic and epigenetic changes and their associations with T2D
- Hypothetical smart targeted nano-delivery system modulating the Wnt signaling pathway for promoting  $\beta$ -cell growth and development
- Hypothetical smart targeted nano-delivery systems exploiting inflammasome and autophagic target points for T2D treatment

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## 1 Introduction

DM is a serious health disorder affecting millions of individuals worldwide and a further 629 million likely to be added to the tally by 2045 [1]. The disorder will be the 7<sup>th</sup> in the cause of global mortalities. DM can be categorized as T1D mainly caused due to deficit in the excretion of insulin and T2D which is a result of abnormal insulin secretion/ action or improved hepatic glucose production [2, 3]. There are copious facets that chip in towards aetiology of T2D and are well explained in biochemical, molecular, and cellular aspects. Chaudhury et al. have put forth that, T2D is modulated by eight main defects called ominous octet [4]. These eight core defects are dysfunction of the neurotransmitter, low uptake of glucose, amplified GNG in hepatocytes, decreased incretin effect, decreased insulin production, increased lipolysis, increased secretion of glucagon, and increased glucose reabsorption [5].

The disease is preliminarily detected through changes in hyperglycemia, macrovascular complications (cardiovascular disorders, stroke, and peripheral vascular complications), and consequential microvascular complications (retinopathy, neuropathy, and nephropathy) [6]. Current therapeutics are limited to drugs that can normalize defects starting with elevated insulin secretion by sulfonylureas and meglitinide. Use of Biguanide and thiazolidinedione to enhance insulin sensitivity through activation of AMPK and PPAR- $\gamma$  receptor respectively are an effectual line of action but have some limitations. Amplified activation of the incretin pathway by DPP-4 inhibitors, SGLT inhibitors, and GLP-1 RAs are reported to be effective with limited or no side-effects [7]. Activation of insulin receptors by insulin bolus insulins, basal insulins, and premixed insulins though not cheap are efficient and available for the common man.

These limitations and side-effects can be neutralized if the cellular and molecular etiology of the T2D is properly comprehended. Moreover, a better understanding of the molecular pathogenesis of T2D can be achieved by dismantling the intricate pathophysiology of T2D in terms of emerging cellular and molecular cascades like inflammasome, autophagy, genetic and epigenetic modifications [8–15]. An in-depth investigation in T2D associated with these molecular and cellular cascades may lead to the development of novel diabetic markers and target points for future therapeutic interventions [16, 17]. Further, transforming these target points into viable therapeutic option requires a customizable, biocompatible delivery vehicle where nanotechnology appears to be the most formidable strategy [18, 19]. The developments made in the current decade and the expeditious evolution of nanotechnology, bridges currently developing applied branches of science and treatment of T2D. Formulating such cutting-edge nano-based products like nanocarriers, nanosensors and nanotools of heterogeneous utilities have radically transformed the height and depth of scientific innovation. Their inimitable

and astonishing characteristics like nano-size, lighter weight, higher strength, and surface area, superior control of light spectrum convey their wide application in multidisciplinary areas [8]. Additionally, biocompatible properties like non-immunogenicity, non-toxicity, sustainability to physiological pH and temperature, control release, target-specific delivery, and action also make them a unique and potential candidate in biomedical application [20, 21]. Considering the benefits and competent medication of nanoparticles towards the mediators/ modulators of T2D, the current review highlights and presents the ventures of the nano-targeting system on finding the euphoria within molecular pandemonium represented in the form of the inflammasome, autophagic, genetic and epigenetic. Different types of nano-delivery systems currently exploited in diabetic research are introduced and some of these researches are listed in a tabular format within the review. Further, the paper describes the conventional commercially available antidiabetic drugs and emerging cellular pathways such as inflammasome, autophagy, genetic, and epigenetic changes at the molecular level and their association with T2D. Moreover, in the review, an effort has been made through hypothesizing novel nanotechnological based smart nuclear targeted nano-delivery systems as therapeutic strategies. The strategy exploits previously described inflammasome where inhibition of NLRP3 inflammasome by antisense oligonucleotide is described [9, 22–24]. Likewise, the nuclear targeted nano-delivery system is designed to induce autophagy by delivering antioxidant molecules for neutralizing ROS which might affect the Atg3/Atg7 complex [11, 12, 25, 26]. A strategy is also provided to promote  $\beta$ -cell growth and development by targeted nano delivery system which could induce the Wnt signaling pathway by inhibiting Gsk3 $\beta$ . Lastly, the paper provides several autophagic and epigenetic factors that can be further exploited for future diabetic researches. These hypothetical nanotechnological based therapeutic strategies may be helpful for the advancement in engineering future therapeutic approaches in T2D.

## 2 Factor inducing $\beta$ -cell failure or loss in type-2 diabetes

### 2.1 Molecular aetiology

Pancreatic  $\beta$ -cell failure as a corollary of tangential IR, declining  $\beta$ -cell response, and compromised synchrony of hepatic GNG are the broad characteristics of T2D [31]. Adapter proteins transduce the signal from insulin receptors towards downstream cascade furnishing IR in T2D [32]. Under normal conditions, the binding of insulin to extracellular  $\alpha$ -subunit of the heterotetrameric glycoprotein of insulin receptor and translocation of GLUT4 to the plasma membrane for glucose

influx and triggering of glycogenesis is described in Fig. 1 [27, 28, 33]. Nuclear localization of  $\beta$ -catenin through the Wnt signaling pathway is another important factor as it interacts with TCF/LEF TF regulating *Pitx2* gene transcription which otherwise may result in mediation and degradation of  $\beta$ -catenin [29, 34, 35] (Fig. 1). Molecular alteration in any of the above mentioned intermediate signaling molecules or TFs may lead to failure and loss of  $\beta$ -cell.

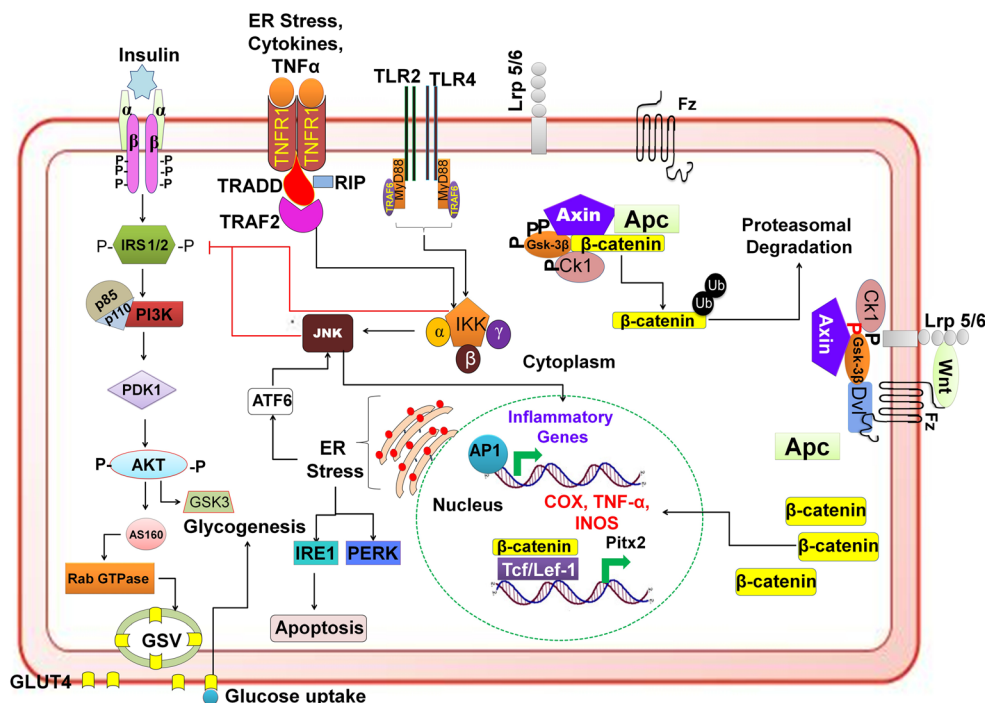
### 2.2 Genetic aetiology

Predisposition at specific genes by default orchestrates an unambiguous consequence leading to malfunctioning of  $\beta$ -cell response or death. Some of the recent investigations suggest that TF like *Pdx1* and *FOXA2* genes are the chief regulator of  $\beta$ -cell maturation [36–38]. MODY, pancreas agenesis or diabetes susceptibility arises as a post mutation consequence in humans at cis-regulatory consensus binding sites of these genes [36]. *Pdx1* along with PTF1A is fundamental for the

growth and maturity of the pancreas [39]. Other factors like TFs like *FOXA1/2*, *SOX9*, *HNF 1 $\beta$* , *Ngn3*, *Hes1*, *Pax4/6*, and *GATA4/6* are also known to orchestrate an intense role in pancreatic development [40–45].

### 2.3 Environmental variables

Environmental factors specifically nutrients and the supply of oxygen plays an imperative role in pancreatic development. A decrease in  $\beta$ -cell mass and increase secretion of fetal corticosterone on the ingestion of low energy diet was evidenced in past investigations, where deprived development of  $\beta$ -cell mass was concurrent with a diminishing number of NGN3- and *Pdx1*-expressing cells [46]. At low  $pO_2$ , the cell undergoes elevated angiogenesis and erythropoiesis with a simultaneous shift towards glycolysis. It is observed that under obese conditions chronic hypoxic state is amalgamated with suppressed NO bioavailability, progressing to T2D [47]. Data also suggests that alteration in any



**Fig. 1** Molecular aetiology of insulin resistance. Binding of insulin to its receptor results in their autophosphorylation of IRS-1/2 (insulin receptor substrates), which activates phosphoinositide 3-kinase (PI3K). This results in activation of P3 dependent kinase-1 (PDK-1) and AKT/Protein Kinase B which guides the translocation of GLUT4 transporter from glucose transport vesicles (GSV) to cell membrane. The activation of C-Jun N-Terminal Kinase (JNK) and Insulin Kappa B Kinase (Ikk) by cytokines, TNF $\alpha$ , Endoplasmic reticulum stress (ER Stress) etc. also leads to negative regulation of insulin signalling pathway. Different Toll like receptors (TLR2, TLR4) are also indulged in insulin resistance by activating MYD88 (myeloid differentiation primary response gene) and TRIF (TIR domain containing adaptor inducing interferon-b ). ER stress activates AFT6 (activating transcription factor 6), IRE-1 (inositol

requiring endonuclease-1) and PERK (pancreatic endoplasmic reticulum kinase-1) which leads to apoptosis. On other side, binding of Wnt ligand to its receptor called Frizzleds (Fz), triggers a signaling cascade that results in the stabilization and nuclear localization of  $\beta$ -catenin whose interactions with T cell-specific factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors control transcription of target genes like *Pitx2*. However, in the absence of Wnt signaling, cytoplasmic  $\beta$ -catenin in Wnt-responsive cells is processed to proteasomal degradation by a heteromeric protein complex containing Axin, glycogen synthase kinase 3 (GSK-3), and other proteins which together is known as  $\beta$ -catenin degradation complex. Wnt signalling regulates cell proliferation in pancreatic tissues. Inspired from [27–30]

physiological concentrations of HIF1 $\alpha$  may lead to inappropriate  $\beta$ -cell function and affect the release of insulin [30] (Fig. 1).

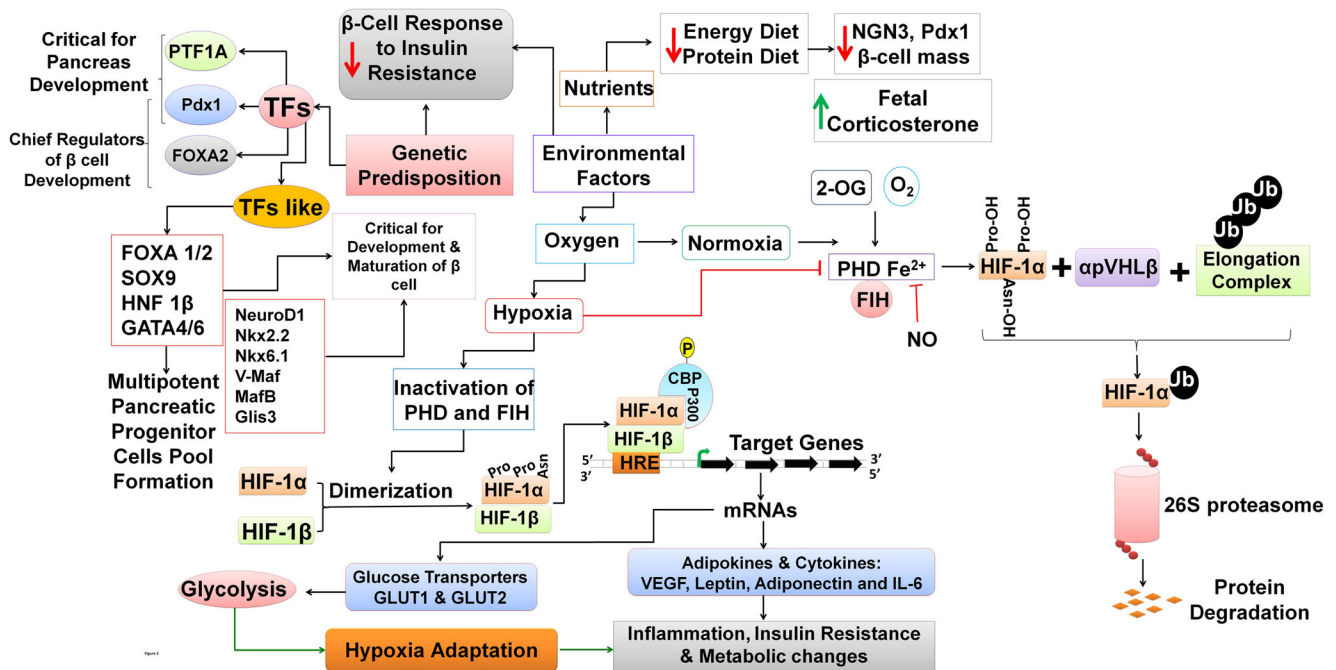
## 2.4 Biochemical erratic

Evaluation of GNG indicated that any form of compromised management in GNG may cause the failure of  $\beta$ -cell and ultimately malfunctioning of insulin action [48]. Besides pancreatic  $\alpha$ -cells, multiple tissues and cell types such as adipose tissue, skeletal muscle, and brain are also involved in indirect gluconeogenic suppression. Transcriptional regulators like FOXO1- 3, 3a, 4, and 6, along with CREB, CREBH, PGC-1 $\alpha$ , glucocorticoid receptor, sterol response element-binding protein (SREBP), STAT3, and DAX1 have also revealed to contribute towards the regulation of GNG [48] (Fig. 2). Additionally, prolonged exposure of glucose and free fatty acids are observed to cause  $\beta$ -cell dysfunction leading to cell apoptosis in T2D.

## 3 Pharmacological treatments available for reversal of type-2 diabetes

Pharmacological treatments for T2D could be segregated into the following types sulfonylureas and meglitinides, biguanide, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, DPP-4 inhibitors, sodium-glucose transporter, inhibitors, GLP-1 receptor agonists, and prandial, basal, and premixed insulin [7] (Fig. 3).

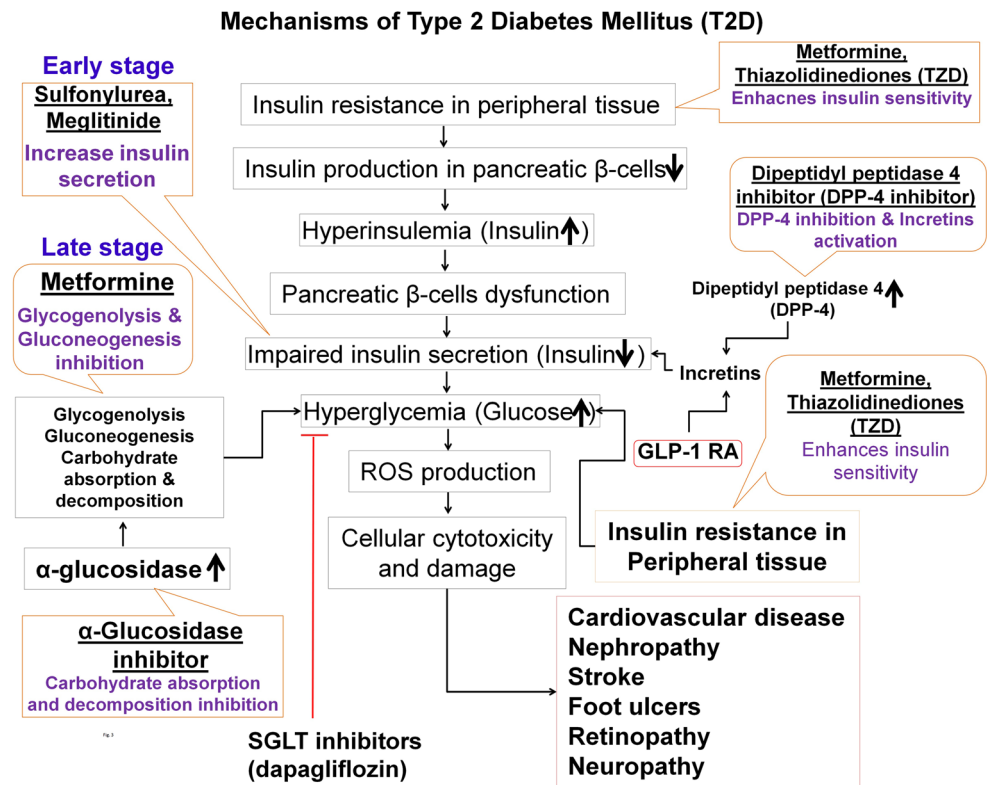
- Sulfonylurea is a stimulator for pancreatic beta cells to secrete insulin by activation of SURs present at the  $\beta$ -cell membrane. The propinquity of SUs varies with different SURs present in potassium ATP dependent channels. Meglitinides is a drug with a similar mechanism which includes repaglinide and nateglinide.
- Metformin a drug type of biguanide that inhibits hyperglycemia by reducing IR, triglycerides formation, hyperinsulinemia, and HbA1c. Further, boosts high-density lipoprotein level by simultaneously lowering



**Fig. 2** Role of genetic predisposition and environmental factors in declining  $\beta$ -cell response to insulin resistance. Different transcription factors (TF) and TFs like viz. Pancreatic Duodenal Homeobox 1 (Pdx1), Forkhead Box A2 (FOXA2), Pancreas Transcription Factor 1A (PTF1A), FOXA1/2, Sex Determining Region Y-box 9 (SOX9), Hepatocyte Nuclear Factor (HNF) 1 $\beta$ , GATA-binding protein (GATA4/6), Neuronal Differentiation 1 (NeuroD1), Nk class of Homeodomain-encoding genes 2.2 (Nkx2.2), Nkx6.1, V-Maf musculo-aponeurotic fibrosarcoma oncogene family protein B (MafB) and Gli-Similar 3 (Glis3) are critical regulator of  $\beta$ -cell development, maturation and function in pancreas. Among nutrients, ingestion of low protein and low energy diet lead to reduction in number of Neurogenin-3 (NGN3)-

and Pdx1-expressing cells, decrease in  $\beta$ -cell mass and increase secretion of fetal corticosterone. Hypoxia plays role in stabilization/destabilization of Hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) by inhibiting Prolyl Hydroxylase Domain enzymes (PHD) & Factor-inhibiting hypoxia-Inducible Factor (FIH) which otherwise used to hydroxylate HIF-1 $\alpha$  for their proteasomal degradation after its ubiquitination. Inactivation of PHD and FIH under hypoxia facilitates heterodimerization of HIF-1 $\alpha$  and HIF-1 $\beta$  which further with phosphorylated cAMP response element-binding protein- (CREB-) binding protein (CBP) and p300 binds to hypoxia-response element (HRE) in nucleus to up/downregulate several genes including glucose transporters (GLUTs), adipokines, and cytokines for hypoxia adaptation. Inspired from [11, 48, 49]

**Fig. 3** Mechanisms involved in the development and pharmacological treatments of Type-2 Diabetes (T2D). Pharmacological treatments for T2D could be segregated into the following types such as sulfonylureas and meglitinides, metformine and thiazolidinediones,  $\alpha$ -glucosidase inhibitors, DPP-4 inhibitors, sodium glucose transporter (SGLT) inhibitors, GLP-1 receptor agonists. These drugs have specific site of action in pathway of insulin resistance mechanism under T2D. Inspired from [7, 50–53]



- low-density lipoproteins. Besides all these actions, it inhibits glycogenolysis, stimulating insulin-receptor substrate-2, and enhancing glucose transport through GLUT-1 translocation.
- (iii) TZD mainly reverses insulin sensitivity by mimicking ligand of PPAR $\gamma$  expressed on adipocyte, liver, heart, colon, activated macrophages, skeletal muscle, etc. The receptor regulates the metabolism of carbohydrate, lipid, cell proliferation, and glucose homeostasis through elevating fatty-acid uptake in blood maintains  $\beta$ -cell function and survival as well as increased insulin sensitivity [54]. Currently, two TZDs are marketed by the name of rosiglitazone and pioglitazone.
  - (iv) PP4 is a cell surface protein expressed in many specialized cell types, functions as degradation of proteins, cell-cell interaction, inflammation, vascular function, immunity, and transduction pathways activation [50]. According to several recent studies, the reduced DPP4 expression and increased concentration of GLP-1 in circulation results in improved production of insulin, decreased GNG, less glucagon secretion, reduced HbA1c level, and improved glucose uptake. Therefore different forms of DPP4 inhibitors are marketed as drugs such as sitagliptin, saxagliptin, and linagliptin.
  - (v) SGLT inhibitors are another novel therapy for T2D. These transporters regulate glucose homeostasis of SGLT1, T2, T4, and T5. SGLT mediates intestinal glucose absorption and re-absorption of kidney glucose.

- They are expressed in the small intestine, testes, brain, kidney, trachea, prostate, pancreatic  $\alpha$ -cells, and heart. The inhibitors of SGLT2 namely dapagliflozin, canagliflozin, and empagliflozin are approved internationally for T2D patients. These novel antidiabetic drugs promote the lowering of blood glucose and HbA1c level by enhancing renal excretion.
- (vi)  $\alpha$ -Glucosidase inhibitors like acarbose, voglibose, emiglitate, and miglitol act by competitive and reversibility inhibiting the enzyme and prevent the formation of monomeric  $\alpha$ -glucose molecules. They are known to reduce postprandial hyperglycemia and hyperinsulinaemia, insulin sensitivity, and liberation  $\beta$ -cell stress.
  - (vii) GLP-1 is an important antagonist that helps in restoring blood glucose regulation to normal levels by regulation of insulin and secretion of glucagon in Type-2 diabetic patients [55]. GLP-1 receptors have generated interest as they enhance incretin action and are segregated as short-acting (exenatide, lixisenatide) and long-acting (albiglutide, dulaglutide, exenatide, liraglutide, and semaglutide) GLP-1 antagonists affecting both fasting and postprandial glucose [51].
  - (viii) Insulin replacement therapy is a reliable therapeutic option for type-2 diabetic patients with insulin deficiency [56]. The therapy comprises basal or long-acting insulin such as aspart, glulisine, etc. or prandial or rapid-acting/ intermediate-acting commercialized

insulin available as isophane insulin, biphasic insulin aspart, and insulin lispro [7]. Insulin replacement therapy encompassing the above-mentioned insulin or insulin analogs acts by activating insulin receptors to modulate the metabolism of carbohydrates, fats, and proteins.

Though these medications have proved effective against T2D by targeting mostly post-symptomatic and certain molecular aspects specifically  $\beta$ -cell proliferation as well as apoptosis arrest, they have several side-effects. Some of the commonly associated ailments include low BP, skin rashes, weight gain, kidney complications, swelling of ankles, dizziness, diarrhea, anemia, etc. and henceforth needs serious consideration for T2D treatment. Additionally, investigation in the present era mostly focused combination therapy or different formulation therapy of these above-mentioned therapeutics or potent non-thiazolidinedione, selective PPAR- $\gamma$  modulators like INT131 which are still in pipeline [57].

#### 4 Targeted pathways in the development of future drugs against T2D

Cutting-edge advancements in diabetic researches encompass mostly omics studies, high throughput bioinformatic tools, and computational simulation-based biological systems. These dry lab generated sophisticated information to indulge one to venture into the world of miniature dynamic machinery where they unceasingly sustain life as we know it. Such dynamic machinery currently explore to understand T2D can be explained in accordance with inflammasome, autophagy, and epigenetics.

##### 1 Inflammasome

Inflammasome can be described as intracellular sensors consisting of NLRP1, 3, 4, 6, 7, 12, AIM2, and NAIP. Association of inflammation in T2D is initiated after recognition of exogenous and endogenous factors like DAMPs by intracellular sensors. In metabolic disorder, ligand like ASC, accommodating a CARD upon interaction with inflammasome (NLRP1 and 3) through their respective common pyrin domain, is activated and recruited [58]. NAIP/NLRP4 then interacts with CARD domain of caspase-1 to regulate the enzyme and releases the activated forms of cytokines IL-1 $\beta$  and IL-18 after cleavage of pro-IL-1 $\beta$  and pro-IL-18 [22]. Other research has conceptualized that ER stress-mediated activation of IL-1 $\beta$  production by NLRP3 [9, 23]. These pro-inflammatory cytokines in a pleiotropic manner elicits a cellular immune response against DAMPs and also mediates  $\beta$ -cell death [9, 22, 23]. Activation of caspase-1 promotes maturation of GSDMD along with pro-IL-1 $\beta$  and

pro-IL-18, where GSDMD causes pyroptosis via pore formation on the membrane through its N-terminal fragment. Li et al. [59] demonstrated the neuroinflammation as well as pyroptotic and apoptotic cell death of hippocampal neuronal cells mediated by NLRP3 inflammasome induction that further contributes to depression in diabetic patients. However, the involvement of GSDMD induced pyroptosis in the case of  $\beta$ -cell death is needed to be investigated.

There is a number of investigations suggesting the linkage of pro-inflammatory cytokines with T2D. It is evidenced that cytokines like aA-FABP, lipocalin-2, PEDF, resistin, fetuin A, IL-6, IL-8, MCP-1, TNF- $\alpha$  and IFN $\gamma$  contributes to either IR or  $\beta$ -cell death [60]. The blocking of downstream insulin signalling pathway due to reduced phosphorylation of IRS1 represents the mechanism underlying IL-1 $\beta$  mediated induction of IR [61]. Solini and Novak [24] have reviewed the connection of P2X7R in insulin secretion from  $\beta$ -cell and diabetes induced micro- and macrovascular complications. Their review states that subjects with metabolic syndrome, P2X7R expression, and inflammasome activation are higher in adipose tissue often leading to chronic inflammation in WAT. In certain cases of T2D, adipose tissue is assailed by macrophages and other leukocytes, secretes, serine protease like GrB causing local and low-grade chronic inflammation. Therefore, it is understood that increased systemic GrB level could be allied with T2D diagnosis and seconded with elevated expression of IL-6, TNF- $\alpha$ , WISP1 in dysfunctional AT-linked systemic inflammation [62].

Experimental observation concludes that patients with T2D display subclinical inflammation, characterized by increased circulating levels of hs-CRP, TLRs, and other mentioned systemic inflammatory mediators [63]. Further reports also state that signal transduction cascade specifically MAP kinase and NF $\kappa$ B activity plays a discrete function in the secretion of the above-mentioned cytokines. Therefore it could possible to target inflammation to ameliorate T2D and the related micro- and macrovascular complications [64]. The recent data presented by Rai et al. [10] manifested the anti-inflammatory effect of metformin and resveratrol in the type-2 diabetic cells.

##### 2. Autophagy

The molecular degradation system within the cell known as autophagy, not only degrades specific proteins but also breaks down lipids, DNA, and RNA by delivering them to lysosome [65]. Like inflammation, association of autophagy with T2D through ER stress is vastly investigated [66]. Autophagy is a prominent player, amending degradation-regeneration inside cellular system by providing continuous flow of raw materials for anabolic process. The ambiguous function of autophagy in cellular homeostasis, or autophagic clearance of toxic cellular components through aggresomes is spectacular in itself.

In detailed, autophagosome construction marks the beginning of autophagy originating from ER membranes through four main steps *namely* initiation, nucleation, elongation, maturation and fusion which are synchronized by autophagy-related genes (*Atgs*) [25]. Instigation of autophagy begins with activation of Ulk1 complex which mediates phosphorylation of Atg13, Atg101 and FIP200 with consequential building up of pre-autophagosome [67, 68]. Ulk1 activates Beclin1 complex through phosphorelation resulting in vesicle nucleation [69]. Simultaneously elongation process initiates with enrollment of other essential machinery of the membrane such as p62 or SQSTM1 an ubiquitin cargo-binding protein and Autophagy-related NBR1 protein that acts as partial selective receptor for different substrate in cell. Two other important proteins namely, MAP1 and LC3-I are obligatory for elongation and maturation of autophagosome and Atg12-Atg5-Atg16L1 complex helps to target particular substrates and proteins to the developing autophagosome [70]. LC3-I the cleaved product of pro-LC3 is a cysteine-protease (Atg4), directed to autophagosome membrane, is later activated by E1-like enzyme Atg7 bound to E2-like enzyme Atg3 and gets conjugated to phosphatidylethanolamine forming LC3-II [71]. The mature autophagosome then amalgamates with lysosome by SNARE proteins and Rab7 forming autolysosome that gets degraded in the acidic environment.

Autophagy is controlled through several regulated and inhibitory complexes like AMPK that regulate this complex cascade by activation of Ulk1, and mTORC1 which inhibits Ulk1 by phosphorylation [72]. In nucleation, Bcl2 bind and inhibit Beclin1, while, at lysosomal interphase, v-ATPase if inhibited could severely affect lysosomal biogenesis. mTORC1 are another sets of inhibitory enzymes that inhibits TFEB by phosphorylation and influencing biogenesis of lysosome [73]. TFEB also plays a prominent act in activation of autophagy, where if not phosphorylated, it may translocates into nucleus and clings to CLEAR sequence (a genetic up-regulation and expression of proteins crucial for lysosomal biogenesis) and involved in autophagic pathway. ZKSCAN3 a TF, which unlike TFEB, inhibiting autophagy requiring proteins and severely affects lysosomal biogenesis.

According to current studies Atg7 is highly exploited in induced autophagic activation in animal cell-lines treated with saturated fatty acid. Atg7 induces a lysosomal cysteine protease (cathepsin B) which contributes towards Atg7-induced NLRP3-dependent pro-inflammatory response and aggravates lipotoxicity [26]. Unlike chronic hypoxia, acute hypoxia activates autophagy induction of deacetylase SIRT1, either inhibition of mTORC1 or by deacetylation of multiple components of autophagy machinery such as Atg5, Atg7 and LC3 in T2D [11, 74]. Investigation shows that in prediabetes subjects, causing of T2D could be delayed by an “adaptive” increase in mitophagy which may result in preservation of  $\beta$ -cell function [12]. Therefore, Marasco and

Linnemann [11] in their review stated that mutation in genes essential of mitophagy such as Clec16a, Pdx1, Pink1 and Park2/Parkin may contribute towards progression of T2D. Zummo et al. [75] in their research have developed a therapeutic strategies intervention for T2D by modulating autophagy/lysosomal homeostasis with GLP-1 signaling pathway. Likewise, there are heterogeneous experimentations designed to find novel natural biomolecules that could either autophagy/lysosomal homeostasis or their restoration. Recently Xu et al. [76] found that trehalose a natural non-reducing disaccharide could restore hyperglycemia-impaired autophagy. Current reports suggest downregulation of macroautophagy in  $\beta$ -cells of T2D patients marked by reduced expression of LC3-II marker as well as increased level of p-62 substrate [77, 78]. It is evidenced by Rezaabakhsh et al. [79] that quercetin is a plant flavonol, could endorse autophagy flux by inducing LC3-II, Beclin-1 and increased utility of p62. These investigation made are profound example where, novel therapeutic intervention for treatment of T2D by manipulating at the sub-cellular level.

### 3. Epigenetics

Present investigations have reported that, more than 100 genetic alterations could be linked to progression of T2D, majority of which affects insulin secretion [13]. According to earlier interpretation, epigenetic modifications can be depicted variation inherited somatically within genome, without altering DNA sequence of an organism, whereas epigenomics regarded as complete set of these changes occurring in that particular organism [14]. These modifications of the genome could be represented as a tool that enables stable propagation of gene expression from parents to offspring through histone modification, DNA methylation and non-coding RNAs [15, 80–82].

#### 4.1 Histone modification

Nuclear proteins in histone octamers could be post-translationally modified on any residue. These modifications are known as histone modification, or described as amino termini modification of histone by 18 different post-translational modifications [83–85]. In histone modification, acetylation and methylation in H3 and H4 molecules lysine residues at amino termini are the most studied processes [80, 84]. Unlike histone tail modifications (that influences nucleosome dynamics, chromatin compaction and transcription) histone core modifications were basically indeterminate until recent reports of its effect [86, 87]. Histone core could be modified by acetylation, methylation, citrullination and phosphorylation affecting chromatin structure by modulating histone-histone, histone-DNA and histone-chaperones [88, 89]. Histone modification regulates physiological processes

through transcriptional activation, induced by increased acetylation, while repression through decreased acetylation of histone molecule [84]. Pathophysiology of T2D due to histone methylation is generally induced by transient hyperglycemia that changes NF $\kappa$ B-p65 expression in vascular epithelial cells [90, 91]. Therapeutics in the present era such as GIP and GLP-1 increases global acetylation of H3 at lysine residues 9 and 18, with increase phosphorylation at serine 10. This further increases its association with TFs, phosphor-CREB and with cAMP-response CREB coactivator 2, and targeting IL-1 $\beta$  [80, 92].

#### 4.2 DNA methylation

DNA methylation is a different set of epigenetic regulator, where carbon-5 of cytosine (C) preceding guanine (G) is methylated by DNA methyltransferase. Majority of these C preceding Gs or CpGs are broadly scattered all over the genome [93]. Previously epigenomic studies had revealed that, there are approximately 450,000 CpG sites which is about 1.5% of all CpG sites in human genome [15]. But currently with Infinium MethylationEPIC BeadChip Kit more than 850,000 CpG sites at a single-nucleotide resolution could be studied which is about 2.833% of all the CpG sites in human genome [94]. Further, methylation status of CpG islands within promoter region immensely influences binding affinity of TF to DNA binding sites thereby regulating gene silencing, transcriptional regulation of cellular differentiation in specific tissue, promotes inactivation of X chromosome etc. [95–97]. T2D which was previously contemplated as a nightmare for geneticists due to weak genetic component, is gradually changing as increasing number of associated genes are being discovered lately. It is now accepted that genes like *Ins*, *Pdx1*, (*PPARGC1-alpha*), *Glp1r* and *IL1R1* are hypermethylated in Type-2 diabetic donors [98, 99]. These genes orchestrate significant role in Type-2 diabetic pathophysiology like encoding insulin and are essential TFs both for development and functioning of mature  $\beta$ -cell (*Pdx1*), mitochondrial transcriptional coactivator (*Ppargc1- $\alpha$* ), receptors that stimulates insulin secretion and protects activated  $\beta$ -cell mass (*Glp1R*). Moreover, higher methylation level was associated with reduced mRNA expression in diabetic  $\beta$ -cells as well as higher HbA1c formation indicating critical role of methylation in T2D [100]. Studies involving methylation confirmed that out of 27000 CpG methylated sites in Type-2 diabetic donors, a total of 1649 CpG sites are altered, annotating 843 genes with 102 varied genes. *Cdkn1A*, *Pde7b* and *Sept9* are examples of genes, whose increased expression and decreased DNA methylation in diabetic islets are observed [15, 81].

#### 4.3 Non-coding RNAs

ncRNAs are emerging as novel multipotent regulators of T2D pathogenesis [101–103]. At the dawn of present decade, it is established that ncRNA like miRNAs are only fraction of ncRNA that displays its impact in multiple health disorders including diabetes [104–106]. Functionally there are two major groups of ncRNAs structural and regulatory ncRNAs [107]. Structural ncRNAs are classified as tRNAs and rRNAs whereas regulatory ncRNAs are categorized based on base pair length as short ncRNAs, mid-size ncRNAs and lncRNAs [104, 107, 108]. In T2D pathophysiology, there are three regulatory ncRNAs including two long ncRNAs (linear and circular lncRNAs) and one short ncRNAs *i.e.* miRNAs [102, 103, 106]. Major fraction of  $\beta$ -cell transcriptome constitute of ncRNAs where involvement of miRNAs are well established but the exemplified function of lncRNAs in modulating  $\beta$ -cell is gradually being unveiled in the present scientific era [109–111]. Recently Reichelt-Wurm et al. [112] revealed differential expression pattern of 1746 lncRNAs that was noticeably different from miRNAs associated with diabetes in mouse model. lncRNAs like, *Meg3* regulates and maintains  $\beta$ -cell's identity by adjusting insulin production, programmed cell death and also promotes insulin production in hepatocytes. Zhu et al. [113] demonstrated that promotion of IR by *Meg3* could possibly be elevated via expression of *FoxO1* regulated by *ATF4*, which itself is suppressed by miRNA-214. Similarly, there are number of other lncRNAs like  *$\beta$ -cell long intergenic noncoding RNA 1* (*Blinc1*) that is important for specification and function of insulin-producing  $\beta$ -cell which must be further studied for deeper insight into  $\beta$ -cell failure [114].

#### 5 Nanotechnology based therapy for reversal of type-2 diabetes

Nanotechnology in present era is being orchestrated as an influential amalgamation of heterogeneous scientific fields. Expandability of these nano-systems to be engineered, in a customizable manner to address specific biological problems from multiple fronts is in itself a magnificent achievement. Execution of this idea to devise a therapeutic strategy against diseases and disorders like T2D is slowly catching its drift in present decade. To understand in depth how nanotechnology could combat T2D, it is a basic necessity to know differential types of NPs or nanosystems presently available. For instance, inorganic, organic and hybrid NPs / nanosystems are the three basic categories of NPs or nanosystems. Inorganic NPs are simple metallic NPs and rigid nanosystem in the form of nanospheres, nanocapsule and nanocage. Whereas, organic NPs are extra flexible/ soft organic matrixes like liposomes, dendrimers, niosomes, micelles etc. [115]. Lastly, hybrid



NPs / nanosystems which are most intricately customized nanodelivery systems, widely investigated in present era. These smart nanosystems in simple terms are standardized amalgamation of inorganic-organic, inorganic-inorganic (nanocomposites), and organic-organic nanoparticulated systems (lipid–polymer hybrid NPs) engineered according to the specific requirement or use at targeted site [116].

### 5.1 Inorganic nanoparticles (NPs)/ nanosystems

Inorganic NPs/ nanosystems are either simple metallic NPs like Ag, Au, ZnO, Se, CeO<sub>2</sub> or rigid nanosystem including SiO<sub>2</sub>/TiO<sub>2</sub> nanospheres or nanocapsule and carbon based nanotubes or nanocage. Though possibility to completely cure diabetes using these inorganic NPs/ nanosystems is questionable, but amelioration of the post diabetic effects without any side-effects is not out of reach (Table 1).

In detail when synthesized AgNPs subjected to STZ induced male albino rats a raise in the level of antioxidant enzymes like SOD, Catalase, GPx and GRD was observed [118]. This might indicate that AgNPs could alleviate oxidative stress under diabetic conditions. Kouame et al. [120] recently showed that *Cinnamomum cassia* aqueous extract mediated Green synthesized AgNPs subjected diabetes induced SD male rats, a reduced level of glucose, serum urea, creatinine, glutathione and malondialdehyde was observed. This suggests the possible role of AgNPs in modulating oxidative stress markers and renal function parameters. Green synthesized AuNPs also could alleviate certain post diabetic effects. Evidence suggests that when diabetic albino mice when injected with AuNPs an increases expression of reduced GSH, SOD, CAT, GPx produced [122]. Shilo et al. [124] demonstrated prevention rapid degradation of conjugated insulin, blood glucose concentration in diabetic male BALB/c mice after administration of insulin-coated AuNPs. The study confirmed that insulin-coated AuNPs possesses an adjustable and prolonged effect on hyperglycemia and are potential for diabetic treatment.

Other metallic NPs like ZnONPs synthesized by Hussein et al. [127] showed reduction in blood glucose, maintains in serum insulin and MDA in diabetic male albino rats after NPs ingestion. Nazarizadeh et al. [130] in consecutive year added that ZnONPs could also improves glucose disposal, insulin level, and zinc status and raise levels of lipid peroxidation but in diabetic male Wistar rats. Later, El-behery et al. [131] and Afify et al. [133] demonstrated the efficacy of ZnONPs in restoring architecture of semi-niferous epithelium and significant decrease in HbA1c respectively. Evidence suggesting anti-hyperglycemic activity of SeNPs is slowly coming up lately. Study conducted by Al-Quraishy et al. [134] suggests reduced blood glucose, lipid, cholesterol level, glucose-6-phosphatase activity and an enhanced serum insulin concentration, malic enzyme, hexokinase and glucose-6-phosphate

dehydrogenase activity in diabetic adult male albino Wistar rats after SeNPs treatment. Additionally, alleviation of oxidative stress, improvement in pancreatic islet function and enhanced glucose utilization activity was also observed in diabetic SD rats and Goto Kakizaki rats after insulin-loaded SeNPs treatment [135]. Recently, Deng et al. [137] demonstrated that oral administration of mulberry leaf and *Pueraria Lobata* extracts loaded SeNPs to diabetic SD rats and Goto Kakizaki rats could effectively alleviates the oxidative stress, improve the pancreatic function, and promote glucose utilization by adipocytes. Similarly Abdulmalek and Balbaa [138] showed that HFD/STZ-induced adult male Wistar rats when administered with SeNPs and metformin improves in insulin signaling proteins like pIRS1/pAKT/pGSK-3 $\beta$ /pAMPK was observed.

Over 50% of diabetic patients are affected by neuropathy and presently the impact of CeO<sub>2</sub>NPs in limiting the worsening condition of diabetic neuropathy is promising, as per current research. Studies conducted by Najafi et al. [139] shows that diabetic male Wistar rats when subjected to CeO<sub>2</sub>NPs total thiol molecules, total antioxidant power, ADP/ATP ratio and body weight were recovered. Additionally, a decrease in lipid peroxidation and nociception latency was also observed. CeO<sub>2</sub> nanocubes were efficient in angiogenesis under diabetic condition in Goto Kakizaki rats by interrupting TNF- $\alpha$  secretion at the transcription level, elevated EGF expression and in diminishing inflammatory reaction [141]. Recently, Pascual et al. [144] showed that CeO<sub>2</sub>NPs could also lessen the extracellular ROS and escalating expression of ADIPOQ and I110 in diabetic mouse 3T3-L1 adipocytes. Antidiabetic drugs of protein origin are receiving mounting interest due to their specific functions and fewer side effects. The extensive application of protein drugs are stalled due their intrinsic properties such as structural and physiochemical sensitivity to temperature and pH from an entropic point of view [167]. Current evidence suggests that amphoteric NPs like SiO<sub>2</sub> have limited therapeutic effect but serves as an excellent delivery system for protein based drugs [168]. In relation diabetes Hei et al. [150] designed an intelligent glucose-responsive insulin delivery system based on MSNP loaded with phenylboronic acids as glucose-responsive units and zinc oxide NPs as the capping agents. Hybrid MSNPs-Metformin developed by demonstrated by Patiño-Herrera et al. [151] prevented excessive drug ingest and increased release time of the drug. As per ongoing research, MSNPs are effectively exploited as a delivery system for either synthetic/ natural drug or natural antidiabetic proteins (Table 1).

The same is speculated for carbon based nanodelivery systems like fullerene, carbon nanotubes, carbon nanohorn, grapheme, carbon dots and comparatively related NPs for diagnosis like quantum dots. Recent investigations impact of amino-acid-functionalized GFNPs on db/db diabetic mice showed a promising improvement of their condition. The

**Table 1** Inorganic nano-based approach for type-2 diabetes diagnosis

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
Silver (Ag) AgNPs	AgNPs	<i>Solanum nigrum</i> aqueous extract	Male Wistar albino rats	Reduces blood glucose level and Improves body weight loss	Diabetic treatment	[117]
	AgNPs	-	Male albino rat	Increases activities and mRNA expression levels of SOD, CAT, GPx and GRD	Diabetic treatment	[118]
AgNPs	PGE-AgNPs	<i>Punica granatum</i> leaf extract	-	Inhibits $\alpha$ -amylase and $\alpha$ -glucosidase	Diabetic treatment	[119]
	AgNPs	<i>Cinnamomum cassia</i> aqueous extract	SD male rats	Reduces levels of fasting blood glucose, serum urea, creatinine, glutathione, malondialdehyde, and alanine aminotransferase.	Diabetic treatment	[120]
Gold (Au) AuNPs	AgNPs	<i>Azadirachta indica</i> (L.) peel extract	-	Inhibits $\alpha$ -glucosidase	Diabetic treatment	[121]
	AuNPs	-	Male albino mice	Inhibits ROS and scavenging free radicals	Diabetic treatment	[122]
	AuNPs	H <sub>2</sub> AuCl <sub>4</sub> -chloroaurate/ <i>Cassia fistula</i> aqueous extract	Adult male albino Wistar rats	Decreases serum urea, creatinine, and uric acid through regeneration of renal tubules in diabetic model	Diabetic treatment	[123]
	Insulin-coated AuNPs	H <sub>2</sub> AuCl <sub>4</sub>	Male BALB/c mice	Reduces blood glucose and prevented rapid degradation of insulin	Diabetic treatment	[124]
Zinc Oxide (ZnO) ZnONPs	AuNPs	H <sub>2</sub> AuCl <sub>4</sub> / <i>Chamaecostus cuspidatus</i> leaf extracts	Adult male Wistar mice	Reduces blood glucose level and Improves body weight loss	Diabetic treatment	[125]
	PPE-AuNPs	H <sub>2</sub> AuCl <sub>4</sub> / Pomegranate peel extract-stabilized AuNPs	Adult male BALB/c mice	Reduces fasting blood glucose, renal toxicity indices, and serum. Normalize pancreatic $\beta$ -cell dysfunction. Activates PI3K/ AKT-guided Nrf2	Diabetic treatment	[126]
	ZnONPs	-	Male albino rats	Reduces blood glucose, maintains serum insulin and MDA; improves expression level of IRA, GLUT-2 gene; Increases sperm count and motility	Diabetic treatment	[127–129]
	ZnONPs	-	Male Wistar rats	Improves glucose disposal, insulin levels, and zinc status; lipogram profile and pancreatic antioxidant status; Restores architecture of seminiferous epithelium and Leydig cells	Diabetic treatment	[130–132]
Selenium (Se) SeNPs	ZnONPs	-	Male albino rats	Increase serum insulin and decrease Glycated haemoglobin	Diabetic treatment	[133]
	SeNPs	-	Adult male albino Wistar rats	Decreases fasting blood glucose levels, hepatic and renal function markers High-density lipoprotein cholesterol levels	Diabetic treatment	[134]
	Insulin	-	SD rats and Goto Kakizaki rats	Enhance blood insulin level, alleviate oxidative stress, improve pancreatic islet function, and promote glucose utilization	Diabetic treatment	[135]
	Nano-Sc-B. longum	Nano-selenium-enriched <i>Bifidobacterium longum</i>	C57BL/6 male mice	Decreases blood glucose and body weight, increases in IPGTT, food intake, serum insulin, water consumption and urine output	Diabetic treatment	[136]
MPE-loaded SeNPs	MPE-loaded SeNPs	Mulberry leaf and <i>Pueraria Lobata</i> extracts	SD rats and Goto Kakizaki rats	Alleviates the oxidative stress, improve pancreatic function, and promote glucose utilization	Diabetic treatment	[137]
	SeNPs	Dextrin	Adult male Wistar rats	Decreases fasting blood glucose, improves in insulin signaling proteins pIRS1/pAKT/pGSK-3 $\beta$ /pAMPK	Diabetic treatment	[138]

**Table 1** (continued)

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
Cerium Oxide (CeO <sub>2</sub> ) CeO <sub>2</sub> NPs	CeO <sub>2</sub> NPs	-	Male Wistar rats	Decreases LPO and nociception latency	Diabetic treatment	[139]
	CeO <sub>2</sub> NPs	<i>Momordica charantia</i> aqueous extract	Male Wistar rats	Shows potent anti-hyperglycemic properties	Diabetic treatment	[140]
Well-ordered hexagonal SBA-15 Mesoporous SINPs	CeO <sub>2</sub> Nanocubes	-	Goto Kakizaki rats	Decreases TNF- $\alpha$ protein and TNF- $\alpha$ mRNA. Increase expression of EGF mRNA	Diabetic wound healing	[141]
	CeO <sub>2</sub> NPs conjugated MicroRNA-146a to (CNP-miR146a)	-	Db/Db mice	Decreases inflammation and increases angiogenesis	Diabetic wound healing	[142]
	CeO <sub>2</sub> NPs	-	Male Wistar albino rats	Increase SDF and Nfr2 expression levels	Diabetic treatment	[143]
Silica (Si) based NPs Alginate or chitosan coated silica NPs	CeO <sub>2</sub> NPs	-	Mouse 3T3-L1 adipocytes	Reduces extracellular ROS, Increases expression of Adipoq and Il10	Diabetic treatment	[144]
	Insulin	-	Goblet cells and mucous cells	Shows high contact with mucin	Insulin delivery	[145]
Phenylboronic acid functionalized mesopores zinc oxide nanoparticles as the capping agents MSNPs	Exenatide	-	Male SD rats and ICR mice	Shows a higher drug loading efficiency. Inhibits blood glucose levels	Diabetic treatment	[146]
	Nano-EE	<i>Echinacea purpurea</i> extract loaded Silica Nanoparticle	SD rats	Prevents lipid peroxidation in tissues, improved oxidative stress, insulin resistance and restored liver and kidney function	Diabetic treatment	[147]
SA-Functionalized 4-Carboxyphenylboronic Acid-Modified Mesoporous Silica Nanoparticles SA/CPBA-MSN/INS	Nano-PAC	Petri dish-cultured <i>Anitrodia cinnamomea</i> encapsulated in silica-chitosan nanoparticles	SD rats	Improves hyperglycemia and insulin resistance. Ameliorates morphology of testicular seminiferous tubules, sperm morphology, motility, ROS production, and mitochondrial membrane potential	Diabetic treatment	[148]
	Insulin	NHS and EDC-HCl	-	Sustain normal blood glucose level. Alleviate lipid metabolism disorder and organ damage	Insulin delivery	[149]
Carbon (C) based NPs Fullerene	Insulin	-	Chang Liver cells	Shows positive correlation with the species and concentration of saccharides, stable release rate in the serum and good biocompatibility with liver cells	Insulin delivery	[150]
	Metformin hydrochloride	-	-	Controls the release of drug, metformin release was significantly prolonged	Diabetic treatment	[151]
Magnesium -25 carrying porphyrin-fullerene nanoparticles C <sub>60</sub> HyFn Amino-acid-functionalized GFNPs	Magnesium -25 carrying porphyrin-fullerene nanoparticles	-	Male Wistar rats	Increases animal weight and decreases glucose level	Diabetic treatment	[152]
	C <sub>60</sub> HyFn	-	Male Wistar albino rats	Recovers histopathological changes and significantly increases in Johnsen's testicular score	Diabetic treatment	[153]
Amino-acid-functionalized GFNPs	-	-	db/db diabetic mice	-	Diabetic treatment	[154]

Table 1 (continued)

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
Carbon nanotubes	HY-CNT	-	Male Wistar rats	Prominently decrease hyperglycemia, along with permanent maintaining normal blood sugar levels, normalized the insulin secretory function	Diabetic treatment	[155]
Carbon nanohorn	NA-MWCNTs	-	Hybrid beta-cell line (1.4E7)	Increases the percentage of neoformed trabeculae and restores bone repair	Diabetic treatment	[156]
Graphene	Phosphomolybdic acid/single-walled carbon nanohorn	-	-	Increases insulin release	Non-enzyme glucose sensing	[157]
	Ni <sub>3</sub> S <sub>2</sub> /ionic liquid-functionalized graphene	-	-	Exhibits prominent selectivity, stability and reproducibility	Non-enzyme glucose sensing	[158]
	rGO-isabgol nanocomposite	-	Wistar rats	Sensitive electrocatalytic activity for glucose Oxidation	Non-enzyme glucose sensing	[159]
	CuNP <sub>8</sub> -graphene	-	-	rGO stimulates collagen synthesis, collagen crosslinking, wound contraction, and reduces wound re-epithelialization time	Diabetic wound healing	[160]
	Boronic acid functionalized graphene GONPs	-	Male Wistar albino rats	Fast response time, high sensitivity, facile fabrication	Non-enzyme glucose sensing	[161]
Carbon dots	Biocompatible carbon dots derived from k-carrageenan and phenyl boronic acid	-	-	Restores both infected and non-infected diabetic wounds	Diabetic wound healing	[162]
Quantum dots	Phenylboronic acid-functionalized gra-phitic carbon nitride quantum dots	-	-	The metformin could be adsorbed onto the GO surface initially at chemisorptive pattern followed by physisorption trend	Effective adsorption of antidiabetic metformin	[163]
	Amino-functionalized silicon quantum dot	-	-	Shows bluish green fluorescence and excellent photostability, possesses ultrasensitive detection of sugar in both solution and human serum samples	Anti-diabetic drug release	[164]
	Chitosan-carbon quantum dots	-	-	Shows high quantum yield and sensitivity towards glucose	Glucose sensor	[165]
		-	-	Exhibits good water-solubility, high fluorescence quantum yield and optical stability	Enzyme free glucose sensing	[166]
		-	-	Ideal material uses for immobilization of insulin specific aptamer	Insulin aptasensor	[166]

GFNPs could decrease hyperglycemia, reversed the pancreas islets dysfunctions and normalized the insulin secretory function, improved hepatic IR, inhibition of GNG and increasing glycogenesis in the liver [154]. As these carbon based nanosystems are an emerging platforms for both treatment and diagnosis therefore limited advancement are reported. Table 1 enlists carbon nanohorn, graphene and quantum dots in sensing glucose non-enzymatically, diabetic wound healing by boronic acid functionalized graphene in Wistar albino rats and efficient anti-diabetic drug release by carbon dots [157, 160, 161, 163, 165]. Current antidiabetic research involving inorganic NPs are mostly focused on sensing glucose or insulin [169–172]. Alhazzawi et al. [169], developed a non-enzymatic glucose detection sensor using rGO/NiO nanocomposite that exhibited good sensitivity, selectivity and was repeatable, stable, and economical. Similarly, Lavanya et al. [171] and Inyang et al. [172] also engineered non-enzymatic glucose detection sensors but with pure  $\text{MgNi}_2\text{O}_3$  and  $\text{MgNi}_2\text{-xAxO}_3$  ( $A = \text{Co}$  or  $\text{Zn}$ ;  $x = 2.5, 10, 25$  wt.%) NPs and CuO NPs on a FTO respectively. Both of the detection systems were highly efficient in sensing glucose. Later, an ultra sensitive and highly selective immunochemical insulin detection system based on  $\text{Ag/ZnIn}_2\text{S}_4/\text{RGO}$  quenched by  $\text{Au@SiO}_2$  NPs was developed by Khan et al. [170].

## 5.2 Organic nanoparticles (NPs)/ nanosystems

Though inorganic NPs are efficient delivery systems but they have certain limitations such as rigidity, size dependent toxicity and nano-accumulation after chronic ingestion. To rule out such limitation, beneficiary properties of organic NPs like the ability to be metabolized after unloading their therapeutic contents are being recognized by researchers [95]. The mode of delivery of therapeutics could be modulated by selecting specific design features and chemical requirements for the synthesis purpose. Since, sustained release or burst release kinetics can directly influence therapeutic competence and toxicity of the nanosystem therefore, selection of appropriate component of the organic NPs based on their release properties is of concern [203]. Multiple form of organic NPs are exploited in field of nanomedicine but only certain specific organic NPs are presently being evaluated for their antidiabetic activity. These includes polymeric NPs, lipid based NPs, dendrimers, nesosomes and nanomicelles (Table 2).

Heterogeneous verity of polymers (synthetic and natural) have been identified which greatly contributed towards drug delivery properties such as biodistribution/ bioavailability, biocompatibility, immunocompatibility etc. in biomedical sector [115]. Polymeric NP developed by Fang et al. [179] was efficient for pH based insulin delivery to diabetic SD rats. El-Naggar et al. [180] in a similar manner developed PLA-PEG copolymer NPs for the delivery of natural compound (Curcumin) to diabetic male white albino rats. Positively they

found that the curcumin loaded nanosystem could trigger a remarkable decrease of serum glucose level, reduces the diabetic rate and attenuates liver inflammation, suppress NF- $\kappa$ B activation, COX-2 and TGF- $\beta$  expression [180]. Even the simple form of polymeric NPs like chitosan NPs proves to be efficient in delivery of polydatin to diabetic male Wistar albino rats, which significantly improves body weight and hepatic glycogen contents [178]. Therefore, most of the investigation involving polymeric NPs are diverted towards controlled delivery of antidiabetic therapeutic agents [181–183]. Recently an effort was made by Laddha and Kshirsagar [181] to deliver pioglitazone-a a PPAR- $\gamma$  agonist through topical administration by a surface modified PLGA NPs to posterior section of the eye. The entrap efficiency and release study was done *in vitro* which showed better entrapment efficiency and initial initial burst release followed by controlled release of pioglitazone-a. The *in vivo* delivery efficiency was also experimented on STZ-induced diabetic Wistar rats which showed controlled release of the PPAR- $\gamma$  agonist which had an dose dependent impact on reduction of VEGF concentration in vitreous fluid [181]. Likewise, Arun et al. [182] developed *Thyroscyphus ramosus* derived chitosan nanodelivery system for the delivery of Metformin to STZ-induced diabetic albino Wistar rats, which was proved efficient in delivery. *In vitro* delivery of insulin was attempted by Wong et al. [183] to skeletal muscle cells. The capability to induce glucose uptake in C2C12 and HT29 cell lines by *in vitro* delivery insulin-loaded chitosan NPs showed promising results.

Ongoing advancement in solid-lipid NPs and outstanding efficiency of nanostructured lipid nanocarriers as a biocompatible vehicle in therapeutic delivery have stunned present researchers. Further, their well structured bio-absorbable and biocompatible properties have granted them a unique prospective to explore [204]. Limitations like transportation of therapeutics across major barriers such as BBB are now nullified. Preliminarily investigation on solid-lipid NPs by Sarmiento et al. [184] devised a cetyl palmitate-based solid lipid NPs for insulin delivery to male diabetic Wistar rats. The lipid nanoterapeutic could significantly reduce glucose levels, protects insulin and promote the insulin absorption in diabetic rat [184]. *In vivo* transdermal patches of metformin loaded solid lipid NPs in diabetic rats were significant in sustained decrease in blood glucose level [185]. LMWP-fused growth factors (EGF, IGF-I), and PDGF-A complexed with HA, were encapsulated within cationic elastic liposomes to determine diabetic wound-healing efficiency in Human fibroblast (CCD-986sk) cells, female C57/BL6 mice. Modified growth factor loaded cationic elastic liposomes promoted fibroblast proliferation and the production of procollagen significantly, improves skin permeation, also significantly accelerates angiogenesis rate [186]. Currently lipid based NPs are also extensively experimented for evaluating their efficacy in delivering antidiabetic therapeutic agents [193, 194]. Recently in a

**Table 2** Organic nano-based therapeutic approach for type-2 diabetes

Nanoparticles	Therapeutic agent	Model organism	Mechanistic mode of action	Purpose	References
<b>Polymeric NPs</b>					
Poly( $\epsilon$ -caprolactone)/end- ragit NPs	Aspart	Adult male Wistar rats	Decreases fasted glycemia and improves glycemic response to glucose	Diabetic treatment	[173]
Sol-gel transition of the multilayer NPs	Sol-gel transition of the multilayer NPs	Male C57BL/6 db/db mice	Decreases blood glucose levels	Diabetic treatment	[174]
CMCD-g-CS NPs	Insulin	Kunming mice	Decrease blood sugar	Diabetic treatment	[175]
Trimethylchitosan nanoparticles	Insulin	Male Wistar rats	Decreases TOS, MDA and blood glucose levels, increases TAC	Diabetic treatment	[176]
PEG-PLGA NPs	Exenatide	Human colon carcinoma Caco-2 cells, db/db mice	High encapsulation efficiency, extended hypoglycemic effects and target specific delivery	Improve hypoglycemic effects	[177]
CSNPs	Polydatin	Male Wistar albino rats	Improves body weight and hepatic glycogen contents	Diabetic treatment	[178]
HPMCP	Insulin	SD rats	Exhibits gradient release profile of loaded drug with increase in pH 3.0 to 7.4 also reduce blood glucose levels	Diabetic treatment	[179]
PLA-PEG NPs	Curcumin	Male white albino rats	Triggers decrease in serum glucose level, attenuates liver inflammation, suppress NF- $\kappa$ B activation, COX-2 and TGF- $\beta$ expression	Diabetic treatment	[180]
PLGA NPs	Pioglitazone- $\alpha$ peroxisome proliferator-activated receptor- $\gamma$ agonist	Wistar rats	Dose dependent reduction in vascular endothelial growth factor concentration in vitreous fluid was observed	Importance of peroxisome proliferator-activated receptor- $\gamma$ in man- agement of diabetic reti- nopathy	[181]
<i>Thyrosocyphus ramosus</i> derived CSNPs	Metformin	Albino Wistar rats	Enhanced drug delivery efficacy	Antidiabetic drug delivery	[182]
CSNPs	Insulin	C2C12 cells (mouse myoblasts) and HT29 (human epithelial colorectal adenocarcinoma cells)	Enhanced insulin delivery efficacy with initial burst release and subsequent controlled drug release pattern was observed	Induction of glucose uptake in skeletal muscle	[183]
<b>Liposome</b>					
Cetyl palmitate-based SLN	Insulin	Male Wistar rats	Reduces glucose levels, protects insulin against chemical degradation, promote intestinal absorption of insulin	Diabetic treatment	[184]
M-SLN transdermal patches	Metformin	Male Wistar rats	Decrease blood glucose level	Diabetic treatment	[185]
Cationic elastic liposomes	LMWP-fused growth factors (EGF, IGF-I), PDGF-A-HA complex	Human fibroblast (CCD-986sk) cells, female C57/BL6 mice	Promotes fibroblast proliferation, improves skin permeation, accelerates wound closure rate	Diabetic wound healing	[186]
Cationic liposomes	siRNA	PBMCs	Restores PBMC Lyp function	Diabetic treatment	[187]
Liposomes	Ex-4	Male Sprague-Dawley rats	Improves glycemic response, increases HDL cholesterol levels and decreases LDL	Diabetic treatment	[188]
Nano-bilosomes	Eprosartan mesylate	Wistar rats	Substantial decrease in serum creatinine, urea, and malondialdehyde. Decreases expressions of Angiotensin II type 1 receptor	Diabetic treatment	[189]
Nano-liposomes	RSV	Beta-TC cells		Diabetic treatment	[190]

**Table 2** (continued)

Nanoparticles	Therapeutic agent	Model organism	Mechanistic mode of action	Purpose	References
Myricitrin solid lipid nanoparticles	-	Adult male NMRI mice and myoblast (C2C12) cell	Decreases glucose levels and shows prolonged antioxidant activity against oxidative stress	Diabetic treatment	[191]
NL@Cas9-RNP	Cas9-Ribonucleoprotein	db/db mice	Increases body and muscle weight, improves hyperglycemia, lipid peroxidation, antioxidant defense, $\beta$ -cell's function index and apoptosis	Diabetic treatment	[192]
Nanostructured polymer-based cochleates SLN	Insulin	SD rats	Disrupts expression of DPP-4 gene, reduces liver and kidney damage	Effective transportation of insulin	[193]
Dendrimer PAMAM G4	Pioglitazone	Male albino Wistar rats	The nanostructure was efficient in controlled release, long-term stability of insulin	Control release of pioglitazone	[194]
PAMAM dendrimer G3	-	Sprague-Dawley rats	The nanoparticles displayed low particle size, high encapsulation efficiency, high and prolonged release activity	Diabetic treatment	[195]
PAMAM G4 dendrimers	-	Wistar rats	Reduces blood glucose, and diabetes-induced permeabilization of blood-brain barrier	Diabetic treatment	[196]
Nano-sized PAMAM dendrimers	-	Sprague-Dawley rats	Improves efficiency of impaired respiration	Diabetic treatment	[197]
Niosome Nano-niosome	Embelin	Male Wistar rats	Scavenges excessive blood glucose and minimize the effects of hyperglycaemia	Diabetic treatment	[198]
Niosomes	Gymnemic acid	Albino Wistar rats	Inhibits the epidermal growth factor receptor (EGFR)-ERK1/2-Rho kinase (ROCK), improves vascular remodeling and dysfunction	Diabetic treatment	[199]
Nanomicelle PEG-PLA nanomicelles	Curcumin	Wistar rats	Shows hypoglycemic effect, increases SOD, CAT, and GSH	Diabetic treatment	[200]
PVCL-PVA-PEG nanomicelle	Curcumin	Adult male BALB/C mice	Decreases antioxidant level and pro-inflammatory cytokines	Diabetic treatment	[201]
		Male C57BL/6 mice	Accelerate angiogenesis and fibroblast accumulation re-epithelialization of epidermis	Diabetic wound healing	[202]
			Enhance accumulation of ROS, reduced free radical scavengers, mRNA expressions in inflammatory cytokines	Corneal epithelial diabetic wound healing	

research by Shaveta et al. [194], showed that, PGL conjugated SLNs loaded with pioglitazone an antidiabetic agent for the determination of *in vitro* and *in vivo* drug delivery efficacy via spectrophotometric analysis and in male albino Wistar rats induced with low dose STZ respectively. Their result demonstrated that SLNs had low particle size, high encapsulation efficiency, high and prolonged release activity [194]. Nanostructured polymer-based cochleates [lipid-based polymer] are also being used for delivery purposes of insulin [193]. Khair et al. [193] demonstrates that insulin loaded polymer-based cochleates served as a promising delivery tool verified via *in vivo* delivery efficiency in SD rat model (Table 2).

Well-organized, hyperbranched organic compound such as dendrimers are receiving much attention in current scenario owing to their enhanced properties such as monodispersity, biocompatibility and biodegradability [205]. These compounds are also an extraordinary vehicle for gene, peptide or drugs (natural/ synthetic) delivery at the targeted site [206]. Despite the previous utility in biomedical science, their investigations as a carrier for antidiabetic drugs are now gradually gaining much appreciation. Some of their antidiabetic efficiencies include lessening of blood glucose concentration and reduction of diabetes-induced permeabilization of blood–brain barrier [195]. PAMAM dendrimer G3 could improve efficiency of impaired respiration of diabetic Wistar rat's cardiac cell mitochondria [196]. Presently inhibition of EGFR-ERK1/2-ROCK, improved vascular remodeling and dysfunction were achieved in diabetic male Wistar rats by nano-sized PAMAM dendrimers [198] (Table 2).

Organic non-ionic surfactant-based vesicle like niosome, has emerges as the centre of attraction for current investigators. Though these nano-delivery systems have ample distributed applications in diseases management but their efficacy as an antidiabetic drug carrier is limited. The investigations made showed significant hypoglycemic effect, increases in SOD, CAT, and GSH, along with decreased lipid peroxidation level was obtained by embelin loaded nano-niosome in diabetic albino Wistar rats [199]. Recently it was observed that gymnemic acid loaded niosomes could substantially decreases antioxidant level, lipid levels, and significantly reduces pro-inflammatory cytokines like IL-6, TNF- $\alpha$  and fibronectin levels in Wistar rats [200].

Other organic NPs like nanomicelles which are described as supramolecular assemblage of surfactant molecule distributed in a colloidal liquid that gives rise to a globular micelle ranging in nano-size. Efficacy in their encapsulation, biocompatibility, colloidal stability and prolonged circulation time are some of the important properties of these polymeric micelles [207]. Specifically like PEG-PLA nanomicelles encapsulating curcumin are described to be significant in augmenting re-epithelialization of epidermis and collagen aggregation in the wound area consecutively accelerating angiogenesis,

fibroblast accumulation in diabetic adult male BALB/C mice [201]. Again PVCL-PVA-PEG nanomicelle loaded with curcumin promotes corneal epithelial diabetic wound healing in diabetic male C57BL/6 mice [202].

### 5.3 Hybrid nanoparticles (NPs)/ nanosystems

Inorganic and organic NPs / Nanosystems are efficient but might be extra efficient in a combined form *i.e.* hybrid NPs, which is by far much sophisticated form of NPs/ Nanosystem. Starting from inorganic NPs such as Ag, Au, Se, SiO<sub>2</sub>, CNT, fullerene and graphene oxide towards organic NPs such as polymeric NPs, lipid NPs and niosomes all are been explored for their antidiabetic activity. Hybrid nanosystems can be considered as a trailblazing/emerging technology both diagnosis and therapy of T2D [208, 209].

Diagnoses of diabetes through hybrid nanosystem based therapy are successful only to specific test like detection of glucose in blood. The nano-based advancement in present prospective includes development of sensors like non-enzymatic glucose detection, nano-based glucose sensor and electrochemical glucose detection [211, 213] (Table 3). Dai et al. [214] developed a Cu<sub>2</sub>O–BSA core-shell nanoparticles modified glassy carbon electrode which exhibited good glucose detection with a lowest detection limit, with linear detection range and a high sensitivity along with reliable anti-interference property to uric acid, ascorbic acid, and acetaminophen. Recently Ni NPs-modified graphene–diamond hybrid electrodes was developed by Cui et al. [213] exhibits efficient glucose sensing capacity with higher resolution in detection. Porous NiMn<sub>2</sub>O<sub>4</sub> nanosheet arrays on nickel foam a form of non-enzymatic glucose detection sensor exhibited high sensitivity and a fast response [211]. Further in-depth research is required to further broaden the detection of other biomolecules associated with diabetes like advanced glycation end-products in blood. Over all almost every research conducted related to diabetes including inorganic NPs even at present is also predominantly directed towards development of nano-biosensors for detection of glucose and insulin concentration [215, 216].

Treatment of T2D with the help of hybrid nanosystems is much more efficient due to a specific property that is target specific delivery (Table 3). Curcumin-encapsulated PBLG-PEG-PBLG NPs could effectively alleviate pathological morphological damage of myocardium, increased H<sub>2</sub>S and [Ca<sup>2+</sup>] levels, and unregulated the expression of calcium-sensing receptor, endogenous cystathionine  $\gamma$ -lyase, and calmodulin in diabetic male SD rats [227]. Mukhopadhyay et al. [229] showed that succinylated chitosan-alginate core-shell-corona NPs encapsulating quercetin could maintain glucose homeostasis, significant reduction of blood cholesterol and triglyceride in diabetic male Wistar rats. Delivery of proteins like insulin by mucoadhesive NPs based on mucin-chitosan



**Table 3** Hybrid nano-based approach for type-2 diabetes diagnosis and therapy

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
<b>Diagnosis</b>						
Small Naked Pt NPs Confined Mesoporous Shell of HCS	Pt/HCS	-	-	Electrochemical stability, sensitivity and selectivity	Non-enzymatic glucose detection	[210]
Porous NiMn <sub>2</sub> O <sub>4</sub> nanosheet arrays on nickel foam	NiMn <sub>2</sub> O <sub>4</sub> /NSs@NF	-	-	High sensitivity and fast response	Non-enzymatic glucose detection	[211]
Glucose oxidase complexed Au-graphene nanocomposite	GNP-GOX	-	-	Improves sensitive detection	Glucose Sensor	[212]
Ni Nanoparticle-Modified Graphene-Diamond Hybrid Electrodes	Ni Nanoparticle	-	-	Exhibits good glucose sensing performance	Electrochemical glucose detection	[213]
Ni-Co Hydroxide Nanosheets	Ni-Co Hydroxide Nanosheets	-	-	Shows high selectivity, low detection limit	Electrochemical glucose detection	[208]
Cu <sub>2</sub> O-BSA core-shell NPs modified GCE	Cu <sub>2</sub> O-BSA NPs	-	-	Good glucose detection high sensitivity and reliable anti-interference property to uric acid, ascorbic acid, and acetaminophen	Electrochemical glucose detection	[214]
rGO/NiO nanocomposite	NiO	-	-	Sensor exhibited good sensitivity and selectivity and was repeatable, stable, and economical for non-enzymatic glucose detection	Non-enzymatic glucose detection	[169]
Engineered hydrophobic ZIF-8 crystal based HHNS	Cu NNPns	-	-	High selectivity with low detection limit	Nonenzymatic electrochemical glucose detection	[215]
Pure MgNi <sub>2</sub> O <sub>3</sub> and MgNi <sub>1-x</sub> AxO <sub>3</sub> (A = Co or Zn; x = 2.5, 10, 25 wt.%) NPs	Co doped MgNi <sub>2</sub> O <sub>3</sub>	-	-	The nanocomposit showed high response and low detection limit and fast response/recovery times	Nonenzymatic electrochemical glucose detection	[171]
Ag/ZnIn <sub>2</sub> S <sub>4</sub> /RGO quenched by Au@SiO <sub>2</sub> NPs	Insulin specific antibody NiO NPs	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	-	High selectivity with ultra sensitive in detection	Immunochemical insulin detection	[170]
Polyaniline intercalated NiO nanocomposites	NiO NPs	-	-	nanocomposites provide a ploform for faster electron transfer to the detection of glucose with high sensitivity	Nonenzymatic electrochemical glucose detection	[216]
CuO NPs on a FTO	CuO NPs	-	-	Electrode exhibited high sensitivity and selectivity and was repeatable, stable non-enzymatic glucose detection	Nonenzymatic electrochemical glucose detection	[172]
<b>Therapy</b>						
Liposomes	Selenium	-	Adult female albino Wistar rats	Recover serum glucose, pancreatic malondialdehyde, nitric oxide (NO), TNF- $\alpha$ , and PGF2 $\alpha$ levels	Diabetic treatment	[217]
AuNPs	AuNP-PEG-BRXL	Sodium tetra chloraurate (III) dehydrate NaAuCl <sub>4</sub> /Curdian	PANC-1 cell	Mimics cellular glucose transporter	Artificial Nano glucose transporter	[218]
AuNPs	Core shell Ag@AuNPs	-	Male albino rats	Reduces blood glucose, lipid profile, restore both the high serum insulin level and glucokinase activity	Diabetic treatment	[219]
Cellulose Nanocrystals decorated with AgNPs	AgNPs	<i>Syzygium cumini</i> leaf extracts	Swiss albino mice	Enhances collagen deposition	Diabetic wound healing	[220]

Table 3 (continued)

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
BNP	Insulin	-	R-HepG2 & KKAY mice	Triggers glucose metabolism	Diabetic treatment	[221]
Argpyrimidine-tagged rutin-encapsulated biocompatible (ethylene glycol dimers) NPs	ARG-EG	-	Male Wistar rats	Reduces blood glucose level, total Cholesterol and triglyceride, increment of high density lipoprotein (HDL)	Diabetic treatment	[222]
Calcium alginate microspheres loaded metformin hydrochloride nitosomes and chitosomes	Metformin hydrochloride	-	Male SD rats	Lowers blood glucose levels, improves MTF hypoglycemic effect	Diabetic treatment	[223]
Thiolated CS-MAC modified Dex-Ma	AgNPs	Triethylamine	SD male rats	Antifouling property	Diabetic wound healing	[224]
DOPA- conjugated PLGA-PEGNPs	FK506/DOPA-NPs	-	Male SD rats	Increases the survival time of pancreatic islets in a xenotransplantation model	Diabetic treatment	[225]
Metformin loaded pectin-CS biohybrids NPs	CPMNP	-	Male Wistar rats	Maintains blood glucose level, controls dyslipidemia, enhances up regulation of IRA, and GK receptor expression, down regulate TNF- $\alpha$ and IL-6 in pancreas	Diabetic treatment	[226]
Curcumin-encapsulated PBLG-PEG-PBLG NPs	PBLG-PEG-PBLG	-	SD rats	Alleviates pathological morphological damage of myocardium, increased H <sub>2</sub> S and [Ca <sup>2+</sup> ] levels, endogenous cystathionine $\gamma$ -lyase, and calmodulin	Diabetic treatment	[227]
CS-coated insulin-loaded cationic liposomes	Insulin	-	Swiss albino mice	Increased tissue residence, reduces glucose level	Diabetic treatment	[228]
Succinylated CS-alginate core-shell-corona nanoparticle	Quercetin	-	Male Wistar rats	Maintain glucose homeostasis, reduces blood cholesterol and triglyceride	Diabetic treatment	[229]
Mucoadhesive nanoparticles based on mucin-CS complexes	Insulin	-	Wistar rats	Decrease blood sugar	Diabetic treatment	[230]
Propanoic acid- AuNPs	Pa@AuNPs	<i>Cassia auriculata</i> aqueous extract/ HAuCl <sub>4</sub>	Rat L6 myotubes	Inhibits of protein-tyrosine phosphatase 1B, $\alpha$ -glucosidases, and $\alpha$ -amylase activity	Diabetic treatment	[231]
AuNPs	AuNPs	<i>Smitax glabra</i>	Adult male wistar rats	Reduces blood glucose and serum leptin	Diabetic treatment	[232]
CS loaded curcumin-metal -ZnO complex	Curcumin	-	Adult male Wistar rats	Reduces blood glucose, maintains lipid profile	Diabetic treatment	[233]
Tannic acid/exendin-4/Fe <sup>3+</sup> ternary NPs	TA-Fe <sup>3+</sup>	-	db/db T2D mice	Maintains blood glucose level	Diabetic treatment	[234]
Gliclazide loaded poly D, L-lactide-coglycolide second-generation nanocrystals	PLGA-SGNCs	-	Male albino SD rats	Produce faster release, improve bioavailability and facilitate efficient delivery	Drug Delivery	[235]
Bilayer nanofibrous scaffolds containing Curcumin/ <i>Lithospermi radix</i> extract	Curcumin/ Lithospermi	<i>L. Radix</i>	Male SD rats	Exhibits higher recovery rate and TGF- $\beta$ expression, decreases IL-6 and TNF- $\alpha$	Diabetic wound healing	[236]

**Table 3** (continued)

Nanoparticles	Therapeutic agent	Source/ Catalytic agent/ Reducing agent	Model organism	Mechanistic mode of action	Purpose	References
Insulin- p(AAPBA-b-NVCL) NPs	Insulin	-	Kumming mice	Easy loading and release of insulin with potential impact on blood biochemistry and other organ	Insulin delivery	[237]
TiO <sub>2</sub> /gelatin nanocomposite NPs	-	-	Male rats	Provides advantages in wound healing acceleration and fibroblast proliferation	Diabetic wound healing	[238]
Pio-nanostructured lipid carriers of pioglitazone loaded COL/CS composite scaffold	Col/ CS	-	Male Wistar albino rats	Enhance cell growth, wound contraction and decreases matrix metalloproteinases-9	Diabetic wound healing	[239]
Insulin and nanogels polyelectrolyte complex CA/Gel electrospun mat loaded with berberine	Ins/NGs-PEC	-	Adult male SD rats	Reduces blood glucose level, enhanced absorption of drug	Insulin delivery	[240]
ZnO/Ag nanocomposites	Berberine	-	L929 murine fibroblastic cell line, dult Wistar rats	The mat showed complete epithelialization and less infiltrated polymorphonuclear inflammatory cells	Diabetic foot ulcer treatment	[241]
M-SeNPs-CC H complex nanohybrid system	ZnO	Milk thistle seed extract	Wistar rats	The nanocomposite showed best efficiencies for enhancement of the insulin and HDL-C plasma levels, while effectively reduced the FBG, T-CHOL and T-TG levels in alloxan-diabetic rats	Insulin therapy	[242]
ZnO:Ag NR's	Mupirocin (M) and SeNPs	-	L929 mouse fibroblast cell line, adult male Wistar rats	The nanohybrid system was effective in wound contraction, angiogenesis, fibroblastosis, collagenesis, and proliferation of hair follicle and epidermis	Diabetic wound infection healing	[243]
TA/Al <sub>3</sub> <sup>+</sup> nanoparticle system	Ag	-	db/db mice	Antidiabetic activity is mediated by $\alpha$ -amylase, $\alpha$ -glucosidase and amyloglucosidase inhibition	Antidiabetic and antioxidant activity	[244]
	Liraglutide	-		The nanosystem displayed better control of blood sugar level, weight control, distinctive improvements on reducing cardiomyopathy, including inhibition in lipo-toxicity in the heart, ameliorated oxidative stress and cell apoptosis activities, with reduced tissue toxicity in multiple organs	Improved therapeutic potential due to long-acting glycemic control	[245]

complexes and chitosan-coated cationic liposomes is gaining much attention lately [228, 230]. With the advancement of science, progresses made in the field of nanotechnology especially encompassing hybrid nanodelivery system in diabetic researches are lately being prioritized, essentially due to their unique properties like targeted delivery and tunable release efficiency etc. [18, 241, 243, 245]. Currently hybrid nanosystems like CA/Gel electrospun mat loaded with berberine and TA/Al<sup>3+</sup> NPs systems loaded with liraglutide are being explored for verifying their effect on diabetic complications like diabetic foot ulcer and prediabetic glycemic condition respectively [241, 245]. The therapeutic efficiency of nanostructure loaded berberine L929 cell line in dult Wistar rats showed complete epithelialization and less infiltrated polymorphonuclear inflammatory cells deposition [241]. Whereas the liraglutide loaded nanosystem showed exceptional delivery efficiency in T2D db/db mice [245]. Pouran et al. [242] have experimented insulin therapeutic efficacy of Green synthesized ZnO/Ag nanocomposites in alloxan-induced diabetic Wistar rats. They observed that nanocomposite was efficient in enhancing of the insulin secretion and HDL-C plasma levels, while successfully reducing the FBG, T-CHOL and T-TG levels in diabetic rat model [242]. Lately, in an *in vivo* study was conducted where, the wound healing property of M-SeNPs-CCH complex nanohybrid system was verified on diabetic Wistar rats infected with *Staphylococcus aureus* [243]. The study confirmed that the nanohybrid system was effective in wound contraction, angiogenesis, fibroblastosis, collagenesis, and proliferation of hair follicle and epidermis [243]. In summation it will not be wrong to state that hybrid nano-delivery system holds immense potential in lessening the severity T2D and associated complications. But still advancements in nanotechnological research needs to progress, in refining the current hybrid nano-based therapeutic systems for T2D treatment.

## 6 Future prospective of nanotechnology in reversal of type-2 diabetes

As previously described cutting-edge advancements made in understanding T2D, it clear that dynamic machineries starting with inflammasome, autophagy, and epigenetics could immensely impel the prospect of diabetic therapy. Numerous factors contribute towards aetiology of T2D which are also described in detail previously. Therefore recent investigations must make efforts such as induction of  $\beta$ -cell proliferation and differentiation, regulation of inflammasome, autophagy, and epigenetics to alleviate T2D.

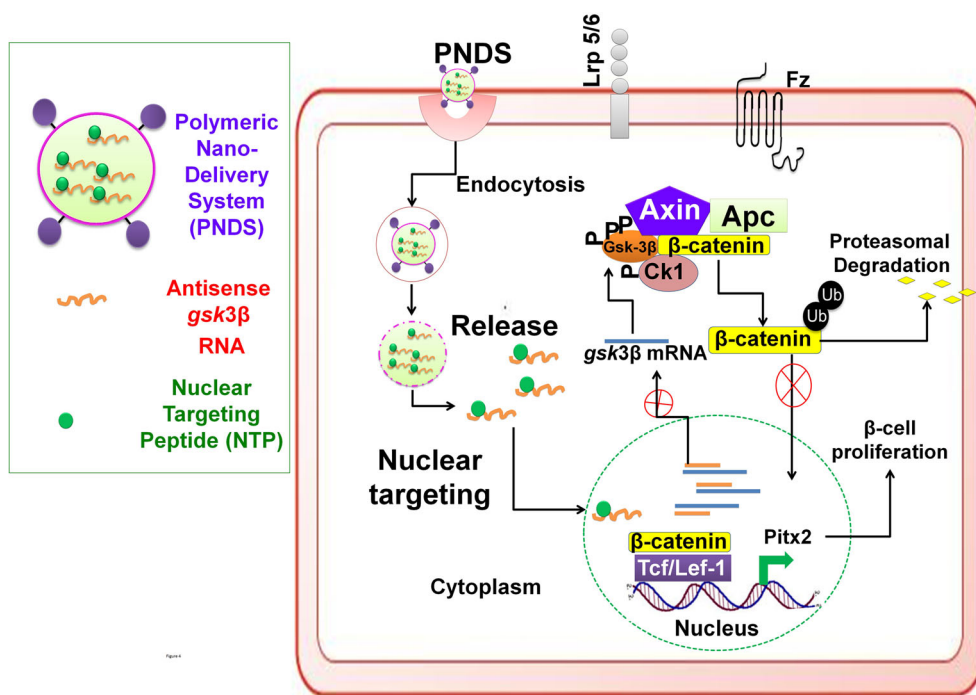
Inducing  $\beta$ -cell proliferation and differentiation by activation of Wnt signaling pathway is one such possibilities that can be achieved through a targeted nanodelivery system. In this signaling pathway, arresting the expression of one

specific component within degradation complex i.e GSK-3, may result in intact  $\beta$ -catenin, which could then translocate into nucleus and promotes  $\beta$ -cell proliferation [246]. A targeted PNDS could be designed for *in vivo* for activation of the Wnt signalling pathway. The PNDS then could be loaded with NTP in conjugation with GSK-3 $\beta$  antisense oligonucleotide for gene silencing of GSK-3 $\beta$ . Later, this PNDS can be tagged with an agonist against pancreatic receptor specific to human  $\beta$ -cell for target-specific delivery. The peptide and antisense oligonucleotide conjugate could migrate into the cells through endocytosis and NTP could lead antisense oligonucleotide into the nucleus. Once inside the nucleus, antisense oligonucleotide could silence GSK-3 $\beta$  gene, which ultimately may inactivate  $\beta$ -catenin destruction complex ensuing in unhindered Wnt signaling pathway and promote  $\beta$ -cell proliferation and differentiation (Fig. 4).

Acknowledging the role of inflammasomes in T2D, an effort can be made for targeted silencing of specific inflammasomes modulators that could effectively alleviate metabolic stress. The present review provides an effective target motive to regulate T2D by nano-based targeting (Fig. 5). A number of investigations also suggest defensive mechanism of inflated autophagy against redox stress in  $\beta$ -cells as a preliminary action [7]. Further, it is also evidenced that under diabetic condition glucolipotoxicity based oxidative stress in  $\beta$ -cells may affect sensitive catalytic thiols of Atg3 and Atg7 which prevents LC3 lipidation, resulting in negative regulation of autophagy [247, 248]. Under such circumstances, natural antioxidants like bioactive phytochemicals could be encapsulated or linked to a  $\beta$ -cells targeted nano delivery system and evaluated for their antioxidant activity and revival of autophagy (Fig. 6).

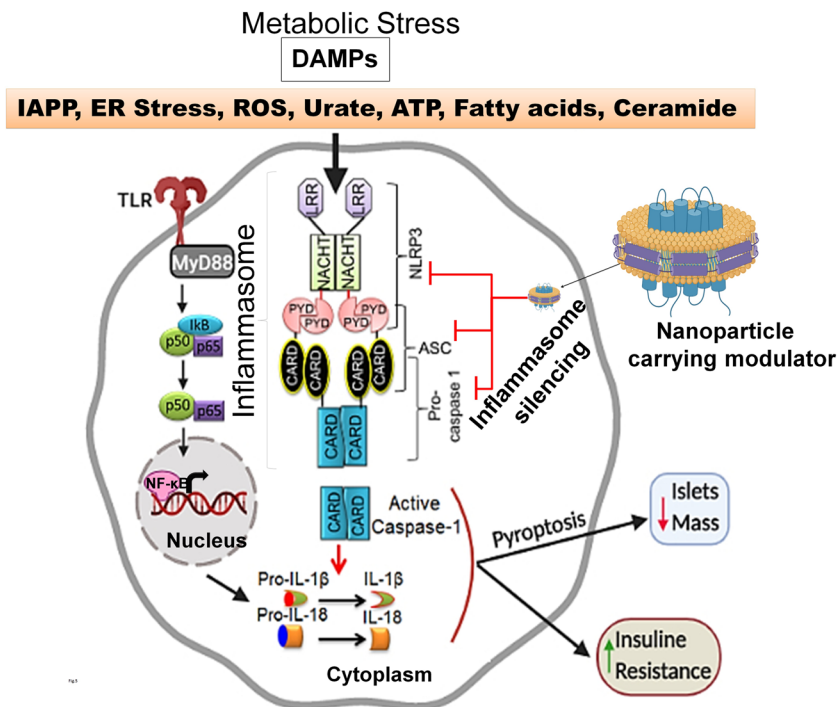
Additionally, within secretory granules under low pH, insulin and proinsulin inhibits aggregation and maintains IAPP in soluble state. Further, in conjunction with glucose stimuli in  $\beta$ -cell, IAPP is coexpressed and co-secreted with insulin, thereby enhanced expression of IAPP aggregate formation can be a likely scenario under high insulin demand (IR) [249]. To remove these aggregation cells mainly deploy three mechanisms which includes ubiquitin protease system, autophagy, and aggresome formation. Out of three majorly investigated enzymes, Zn<sup>2+</sup> metalloprotease named IDE which is generally involved in the clearance of insulin also degrades IAPP aggregations [250, 251]. THE second IAPP degrading enzyme, NEP is a type-2 Zn-containing metalloprotease expressed in diverse cell-type including  $\beta$ -cells could be an alternative target [252]. Lastly, UCH-L1 abundantly expressed in  $\beta$ -cells degrades IAPP by promoting its ubiquitination can also be targeted in therapeutic intervention purposes [253]. Recent research states that autophagy abnormalities specifically *Atg 7* gene in  $\beta$ -cells may lead to the deposition of protein aggregates [254]. Sequestosome 1 (p62/SQSTM1) a multifunctional stress-inducible scaffold

**Fig. 4** *In vivo* activation of Wnt signalling pathway using polymeric nano-delivery system (PNDS). In absence of Wnt molecule, active  $\beta$ -catenin degradation complex degrades  $\beta$ -catenin and suppresses the proliferation of  $\beta$ -cells in Islets of Langerhans. The PNDS mediated targeting and release of antisense RNA (for example, Gsk3 $\beta$ ) in the nucleus could destroy the Gsk3 $\beta$  which is required for stability of degradation complex. In absence of Gsk3 $\beta$ ,  $\beta$ -catenin could be translocated to the nucleus for gene expression. Inspired from [246]



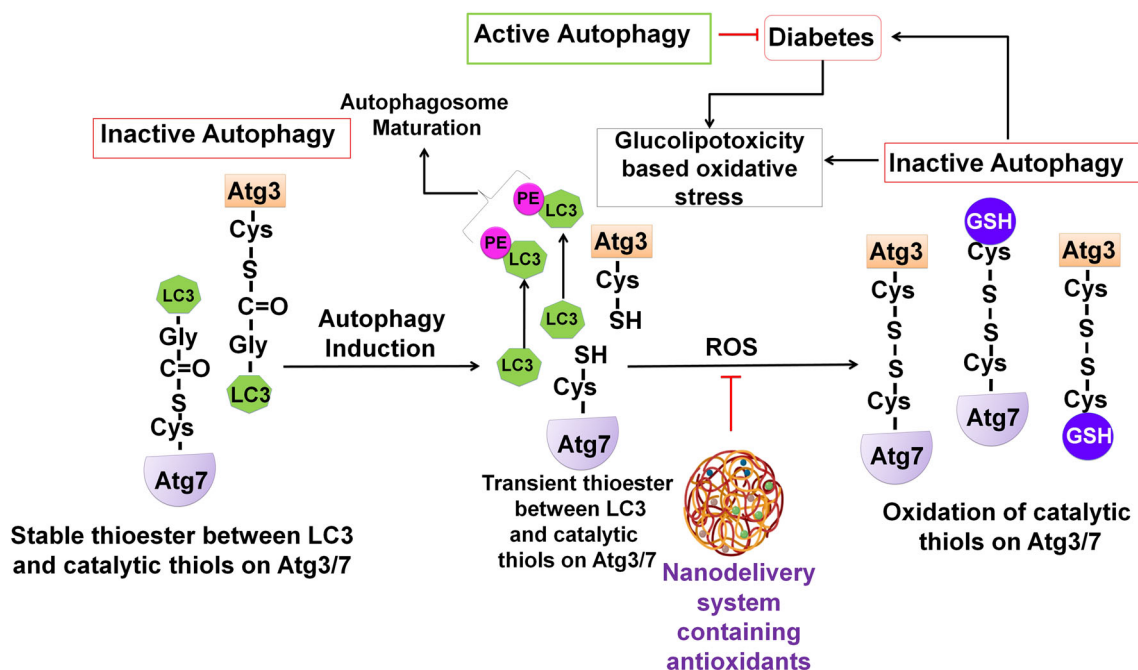
protein can form cytosolic protein inclusion with simultaneous degradation of specific protein clump by aggregaphy

could be an example of such phenomenon [250, 255]. The possibilities of powering these enzymes and other protein



**Fig. 5** The Schematic for the role of NLRP3 inflammasome in type-2 diabetes and its targeting by nanoparticles. Damage associated molecular pattern (DAMPs) such as islet amyloid polypeptide (IAPP), endoplasmic reticulum (ER) stress, reactive oxygen species (ROS), urate, extracellular ATP, fatty acids, ceramide can be recognized by NLRP3 inflammasome in myeloid cells. The assembly of NLRP3 with ASC and procaspase-1 activates inflammasome which cleave CARD domain to release active

caspase-1. Caspase-1 converts pro IL-1 $\beta$  and pro IL-18 in to active IL-1 $\beta$  and IL-18. Such proinflammatory cytokines may induce insulin resistance or reduction in mass of pancreatic  $\beta$ -cells leading to development of diabetes mellitus. The different modulators of inflammasome can be carried by NPs to target the inflammasome in the myeloid cell. Inspired from [9, 22–24]



**Fig. 6** Role of inactivation of autophagy by Atg3 and Atg7 oxidation in Diabetes mellitus. The transfer of LC3 from inactive Atg3 & Atg7 to phosphatidyl ethanolamine (PE) results in maturation of autophagosome and activation of Atg3 and Atg7, which become vulnerable to glucolipototoxicity based oxidative stress under diabetic condition. Under oxidizing conditions, the catalytic thiol group of both Atg3 & Atg7 form intermolecular disulfide bond within same complex or if only a single

catalytic thiol is present within the Atg3/ Atg7 complex, then oxidation will likely lead to stable S-glutathiolation (GSH). Use of targeted nanodelivery system carrying natural antioxidants like bioactive phytochemicals in  $\beta$ -cells can help in neutralization of the reactive oxygen species (ROS) and revival of autophagy for control of diabetes. Inspired from [25, 67, 69, 71]

degradation systems as a therapeutic measure against neural diseases show promising results, investigations in diabetes research might also lead to certain novel findings [251, 256, 257].

Disruption of epigenome homeostatic balance that is deregulation in DNA methylation, histone modifications, and RNA-mediated processes, may cause assorted pathologies impact, finally leading to T2D [15]. DNA methylation patterns within several loci such as *Hnf4A*, *Irs1*, *Kcnq1*, *Pparg*, *Fto*, and *Tcf7L2* are some of the genetic variants persuading to T2D have been acknowledged recently [258]. Like DNA methylation, post-translational modifications to histone proteins such as variation in the levels of histone PTMs such as H3K9ac and H3K4me at key fibrotic, inflammatory, and cell cycle genes, are also concerned in the development of diabetes and its vascular complications [259]. Under the diabetic condition, oxidation results mostly from glucotoxicity and lipotoxicity, affecting the DNA methylation, post-translational modifications to histone proteins. These effects could be reversed preliminarily by countervailing the oxidative stress by implementing the effectiveness of natural antioxidant compounds, delivered through a targeted nanodelivery system. Recently, through wet and dry lab analyses of published reports, it was understood that *Prkar1A* gene is correlated to glucose metabolism, blood coagulation, and insulin signaling and targeted by miRNAs in T2DM. Later

Pordzik et al. [260] observed that miR-30a-5p, miR-30d-5p, and miR-30c-5p are the most extensively regulated miRNAs across all specified ontologies and hence indulged as most promising biomarkers of T2DM to be confirmed in future clinical studies.

## 7 Conclusion

With a present death rate of 5 million per year and the future 7<sup>th</sup> cause of death, diabetes, alone holds a global expenditure of 760 billion US dollars per year. Despite the investment made for the treatment of diabetes, the possibility of a novel therapeutic intervention is questionable and the available commercialized therapeutics demonstrates limitations that need to be addressed. The conceptualized refinement of available commercialized anti-diabetic therapeutics has become the need of the present scientific community. This refinement will be abridged if the amalgamation of present cutting-edge science like nanotechnology is restricted. Additionally, if current evolving knowledge on intracellular modulating factors involved in inflammasome, autophagy, and gene regulating epigenetic changes remains unacknowledged in T2D. Targeting these governing mediators/ modulators with a nano-targeting system could be an effective means for the treatment of T2D. From the present review, advancement in nanoscience for the

reversal of T2D has been highlighted, exploiting cellular and molecular modulating factors like auto-inflammatory, autophagic, genetic, and epigenetic factors. Therefore future research should concern in exploiting some of these strategies mentioned in this review to ensure the probability of devising a smart therapy for the reversal of T2D in near future.

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**Data availability** All data related to the manuscript are available in the form of tables and figures in the manuscript.

## Compliance with ethical standards

**Conflict of interest** RG Kerry, GP Mahapatra, GK Maurya, S Mahari, S Patra, G Das, JK Patra, S Sahoo declare they have no conflict of interest with the manuscript.

**Code availability** Not applicable

**Ethics approval** Not applicable

**Consent to participate** All authors gave their consent to participate in the review.

**Consent for publication** Not applicable

**Abbreviations** (TA)/A13+, Ternary liraglutide/tannic acid; A-FABP, adipocyte-specific fatty acid-binding protein; AFT6, activating transcription factor 6; Ag, Silver; Ag/ZnIn<sub>2</sub>S<sub>4</sub>/RGO, Silver/ZnIn<sub>2</sub>S<sub>4</sub>/reduced graphene oxide composites; Ag@AuNPs, Core shell silver-gold nanoparticles; AgNPs, Silver Nanoparticles; AIM2, Absent in melanoma 2; AMPK, AMP-activated protein kinase; AMPK, AMP-activated protein kinase; ARG-EG, Argpyrimidine-tagged rutin-encapsulated biocompatible (ethylene glycol dimers); ASC, Apoptosis-associated speck-like protein; ATF4, Activating transcription factor 4; Atg 7, Autophagy Related 7; Atgs, autophagy-related genes; Au, Gold; Au@SiO<sub>2</sub>, Gold decorated silicon dioxide nanoparticles; AuNPs, Gold Nanoparticles; BINP, Biomaterialized insulin nanoparticle; BSA, Bovine serum albumin; BSC-dots, Biocompatible carbon dots derived from κ-carrageenan and phenyl boronic acid; C, Cytosine; C<sub>60</sub>H<sub>2</sub>F<sub>n</sub>, Hydrated C<sub>60</sub> fullerene; CA-Gel, Cellulose Acetate/ Gelatin; cAMP, Adenosine 3',5'-cyclic monophosphate; CARD, Caspase activation and recruitment domain; CAT, Catalase; CBP, CREB-binding protein; Cdkn1A, Cyclin-dependent kinase inhibitor 1; CeO<sub>2</sub>, Cerium Oxide; CeO<sub>2</sub>NPs, Cerium Oxide Nanoparticles; CNP-miR146a, CeO<sub>2</sub> NPs conjugated MicroRNA-146a; COX-2, Cyclooxygenase-2; CPMNP, Chitosan and pectin with Metformin nanoparticle; CREB, cAMP-response element binding; CREBH, cAMP-response element binding protein-H; CS-NAC, Thiolated Chitosan- Maleic Acid; CS-ZnO-NC, Chitosan loaded curcumin-metal zinc oxide complex; Cu<sub>2</sub>O-BSA NPs, Copper(I) oxide-bovine serum albumin core-shell nanoparticles; CuNPs-graphene, Cu

Nanoparticles Modified as-grown CVD Graphene; DAMPs, Damage associated molecular pattern; DM, Diabetes mellitus; DOPA, 3,4-dihydroxy-L-phenylalanine nanoparticles; DPP-4, Dipeptidyl peptidase-4; EDC-HCl, N-Ethyl-N'-(3-(dimethylamino)propyl)carbodiimide hydrochloride- hydrochloric acid; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; ER, Endoplasmic reticulum; ERK, Extracellularly Regulated Kinase; EXT, Exenatide; FBG, Fasting blood glucose; FIH, Factor-inhibiting hypoxia-Inducible Factor; FIP200, Focal adhesion kinase family interacting protein of 200; FOXA2, Forkhead Box A2; FoxO1, Forkhead box protein O1; FTO, Fluorine doped tin oxide; Fz, Frizzleds; G, Guanine; GATA4/6, GATA-binding protein; GCE, Glassy carbon electrode; GFNPs, Amino-acid-functionalized gadofullerene nanoparticles; GFNPs, Gadofullerene nanoparticles; GIP, Glucose-dependent insulinotropic-peptide 1; GK, Glucokinase; Glis3, Gli-Similar 3; GLP-1 Ras, peptide-1 receptor agonists; GLP-1, Glucagon-Like Peptide 1; GLP-1, Glucagon-like peptide-1; Glp1r, Glucagon like peptide 1 receptor; GLUT4, Glucose transporter 4; GNG, Gluconeogenesis; GNP-GOx, Glucose oxidase complexed gold-graphene Nanocomposite; GNP-PEG-BRXL, Gold nanoparticle-Poly ethylene glycol-Benzoxaborole; GO, Graphene oxide; GPx, Glutathione Peroxidase; GrB, Granzyme B; GRD, Glutathione reductase; GSH, Glutathione; GSK-3, glycogen synthase kinase 3; GSK-3β, Glycogen synthase kinase 3-beta; GSV, glucose transport vesicles; H3K4me, H3K4 methylation; H3K9ac, H3K9 acetylation; HA, Hyaluronic acid; HAUC14, Tetrachloroauric acid; HbA1c, Glycated hemoglobin; HbA1c, Haemoglobin A1c; HDL, High density lipoprotein; HDL-C, High-density lipoprotein- cholesterol; HFD/STZ, High-fat diet/streptozotocin; HHNs, Hydrophilic hierarchically-porous nanoflowers; HIF-1α, Hypoxia-inducible factor-1α; HNF, Hepatocyte nuclear factor; HPMCP, Hydroxypropyl methylcellulose phthalate; HRE, Hypoxia-response element; hs-CRP, High-sensitive C-reactive proteins; HY-CNT, Carbon nanotubes functionalized with sodium hyaluronate; IAPP, Islet amyloid polypeptide; IDE, Insulin-degrading enzyme; IFNγ, Interferon gamma; IGF-1, Insulin-like growth factor-I; Ikk, Insulin Kappa B Kinase; IL-1β, Interleukin-1 beta; IL-6, Interleukin; Ins, Insulin; Ins/NGs-PEC, Insulin and nanogels polyelectrolyte complex; INS-SeNPs, Insulin-loaded SeNPs; insulin/CMCD-g-CS NPs, Insulin-loaded carboxymethyl-b-cyclodextrin-grafted chitosan nanoparticles; IR, Insulin resistance; IRA, Insulin receptor A; IRE-1, Inositol requiring endonuclease-1; IRS, Insulin receptor substrates; JNK, C-Jun N-Terminal Kinase; K2S2O8, Potassium persulfate; LC3, Light chain 3; LDL, Low density lipoprotein; LMWP, Low-molecular-weight protamine; LMWP, Low-molecular-weight protamine; lncRNAs, Long ncRNAs; LPO, Lipid peroxidation; MCP-1, Monocyte chemoattractant protein-1; MDA, Malondialdehyde; Meg3, Maternally expressed gene 3; Metf, Metformin; miRNAs, microRNAs; MODY, Maturity-onset diabetes of the young; MPE, Mulberry leaf and Pueraria Lobata extracts; mRNA, Messenger RNA; M-SeNPs-CC H, Selenium-Chitosan-Mupirocin complex nanohybrid system; M-SLN, Solid lipid NPs; MSNPs, Mesoporous silica nanoparticles; MYD, Myeloid; NaAuCl<sub>4</sub>, Sodium tetra chloraurate (III) dehydrate; NAIP, Neuronal apoptosis inhibitory protein; NA-MWCNTs, Nicotinamide-functionalized multiwalled carbon Nanotubes; Nano-EE, Echinacea purpurea extract loaded Silica Nanoparticle; Nano-PAC, Petri dish-cultured Antrodia cinnamomea Nanoparticle; NBR1, Neighbor of BRCA1; ncRNAs, Non-coding RNAs; NEP, Neprilysin; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NGN3, Neurogenin-3; NHS, N-hydroxysuccinimide; Ni<sub>3</sub>S<sub>2</sub>, Nickel subsulfide; NiMn<sub>2</sub>O<sub>4</sub>, Nickel-manganese spinel oxide; NiMn<sub>2</sub>O<sub>4</sub>NSs@NF, Porous NiMn<sub>2</sub>O<sub>4</sub> nanosheet arrays on nickel foam; NL@Cas9-RNP, Nano liposomal core Cas9-Ribonucleoprotein; NLRP1, Nuclear localization leucine-rich-repeat protein 1; NO, Nitric oxide; NPs, Nanoparticles; NTP, Nuclear targeting peptide; p(AAPBA-b-NVCL), Insulin-loaded poly (3-acrylamidophenylboronic acid-block-N-vinylcaprolactam) nanoparticles; P2X7R, Purinergic type 2X7 receptor; Pa@AuNPs, Propanoic acid gold nanoparticles; PAMAM, Poly (amido) amine; PANC-1, Primary Pancreatic Cancer; PBLG-PEG-PBLG, poly (gamma-benzyl l-

glutamate)-poly (ethylene glycol)-poly (gammabenzyl l-glutamate); *PBMCs*, Peripheral blood mononuclear cells; *PC*, Prohormone convertase; *Pde7b*, cAMP-specific 3', 5'-cyclic phosphodiesterase 7B; *PDGF-A*, Platelet-derived growth factor-A; *PDK-1*, P3 dependent kinase-1; *Pdx1*, Pancreatic duodenal homeobox 1; *PE*, Phosphatidyl ethanolamine; *PEDF*, Pigment epithelium-derived factor; *PEG-PLGA*, Polyethylene glycol-poly(lactic-co-glycolic acid); *PERK*, Pancreatic endoplasmic reticulum kinase-1; *PGC-1 $\alpha$* , - Peroxisome proliferator-activated receptor gamma co-activator-1 $\alpha$ ; *PGE*, Punica granatum leaf extract; *PGF2 $\alpha$* , Prostaglandin F2 $\alpha$ ; *PHD*, Prolyl Hydroxylase Domain enzymes; *phosphor-CREB*, Phosphorylated cAMP-response element-binding protein; *PI3K*, Phosphoinositide 3-kinase; *Pio*, Pioglitazone hydrochloride; *Pio-NLC-COL-CS*, Pioglitazone hydrochloride (Pio)-Nanostructured Lipid Carriers of Pioglitazone Loaded Collagen/Chitosan Composite Scaffold; *PLA-PEG*, Polylactide-poly(ethylene glycol); *PLGA-SGNCs*, Glielazide loaded poly D, L-lactide-coglycolide second-generation nanocrystals; *PNDs*, Polymeric nano-delivery system; *PPARGC1-alpha*, Peroxisome proliferator-activated receptor gamma co-activator 1-alpha; *PPAR- $\gamma$* , Peroxisome proliferator-activated receptor gamma; *Pt/HCS*, Platinum Nanoparticles in Shell of Hollow Carbon Spheres; *PTF1A*, Pancreas transcription factor 1A; *PTMs*, Post-translational modification; *PVCL-PVA-PEG*, Polymer polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; *PVCL-PVA-PEG*, Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; *rGO*, Reduced graphene oxide; *rGO/NiO*, Reduced graphene oxide and nickel oxide; *ROS*, Reactive oxygen species; *rRNAs*, Ribosomal RNAs; *SA/CPBA-MSN/INS*, SA-Functionalized 4-Carboxyphenylboronic Acid-Modified Mesoporous Silica Nanoparticles; *SD*, Sprague Dawley; *SDF*, Stromal cell-derived factor; *Se*, Selenium; *SeNPs*, Selenium Nanoparticles; *Sept9*, Septin-9 - Homo sapiens; *SGLT*, Sodium-linked glucose transporter; *SGLT*, Sodium-linked glucose transporter; *SiNPs*, Silica based nanoparticles; *SiO2*, Silicon Dioxide; *siRNA*, Short interfering RNA; *SIRT1*, NAD-dependent deacetylase sirtuin-1; *SLN*, Cetyl palmitate-based solid lipid nanoparticles; *SOD*, Superoxide Dismutase; *SOX9*, Sex determining region Y-box 9; *SQSTM1*, sequestosome 1; *SREBP*, Sterol response element-binding protein; *STAT3*, Signal transducer and activator of transcription 3; *STZ*, Streptozotocin; *SU*, Sulfonylurea; *SURs*, Sulfonylurea receptors; *T1D*, Type 1 diabetes; *T2D*, Type-2 diabetes; *TAC*, Total antioxidant capacity; *TCF/LEF*, T cell-specific factor/lymphoid enhancer-binding factor; *TCF/LEF*, T cell-specific factor/lymphoid enhancer-binding factor; *T-CHOL*, Total cholesterol; *TF*, Transcription factors; *TFEB*, Transcription factor EB; *TGF- $\beta$* , Transforming growth factor- $\beta$ ; *TiO2*, Titanium Dioxide; *TLR*, Toll like receptors; *TLRs*, Toll-like receptors; *TNF- $\alpha$* , Tumor necrosis factor-alpha; *TOS*, Total oxidative status; *TRIF*, TIR domain containing adaptor inducing interferon-b; *tRNAs*, Transfer RNAs; *T-TG*, Total triglyceride; *TZD*, Thiazolidinedione; *UCH-L1*, Ubiquitin carboxyl-terminal hydrolase L1; *Ulk1*, unc-51-like kinase 1; *v-ATPase*, Vacuolar ATPase; *WAT*, White adipose tissue; *WISPI*, Wnt1-inducible signalling pathway protein 1; *ZKSCAN3*, Zinc finger protein with KRAB and SCAN domains 3; *ZnO*, Zinc Oxide; *ZnO/Ag*, Zinc oxide and silver; *ZnO:Ag NR's*, Silver (Ag) doped ZnO nanorods; *ZnONPs*, Zinc Oxide Nanoparticles;  *$\beta$ linc1*,  $\beta$ -cell long intergenic noncoding RNA 1

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