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Nanotechnology and nucleic acid nanoparticles for treatment of metabolic disorders

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ABSTRACT

Metabolic disorders result from inborn and acquired dysfunction of organs and tissues that are responsible for producing energy in the body. These diseases are now among the most prevalent maladies in the world. Treatment often requires addressing individual conditions, including obesity, diabetes, and liver diseases with a combination of multiple drugs. Accumulating evidence shows that the defects or overexpression of some specific genes in the diseased organ cause such diseases. Therefore, advanced options are required to control them at the molecular level. In this review, we highlight the current approaches of nanotechnologies, especially for delivering exogenous nucleic acid nanoparticles to treat metabolic disorders. We also summarize the mechanisms of how various nucleic acid nanoparticles have been utilized, the trends, and the potential applications of these materials in metabolic disorders. Greater knowledge of nanotechnologies and nucleic acid particles may pave the way to cure these prevalent diseases effectively.

Abbreviations

BMI	Body mass index
T2D	Type 2 diabetes
T1D	Type 1 diabetes
QCT-AgNP	Silver nanoparticles created Querceti
SC-AuNP	Salacia chinensis-containing gold nanoparticles
L-Rnano	Resveratrol-loaded nanoparticles to form ligands
GDNP	Ginger-extracted nanoparticles

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NO	Nitric oxide
PLGA	Poly lactic-co-glycolic acid
siRNA	small interfering RNA
mRNA	messenger RNA
miRNA	microRNA
ASOs	Antisense oligonucleotides
pDNA	plasmid DNA

1. Introduction

Metabolic disorders, in which metabolic processes are abnormally disrupted, have become one of the most serious challenges for health systems worldwide. The prevalence of metabolic disease has reached the levels of a pandemic [1–3]. The dysregulation of glucose, lipids, and energy-producing mitochondria in metabolic disorders contributes to redox imbalance and cellular dysfunction, leading to dysfunctional cells and tissues [4]. In mitochondria dysfunction-related diseases such as Leigh syndrome or Alpers-Huttenlocher syndrome, the mitochondria fails to produce sufficient energy to support the normal functions of cells and the entire body [5,6]. Several health issues are associated with metabolic disorders, such as hypertension, various types of cancer, cardiovascular diseases, ischemia, and reproductive abnormality [7,8]. The medical cost of treating such diseases in the USA is expected to reach $66 billion in 2030 [7]. Productivity loss caused by hospitalization and low life expectancy have been estimated to be $74 million and $444 million in the USA, respectively [7]. Obesity alone causes 2.8 million deaths per year and roughly 35.8 million disability-adjusted life years, according to data from the World Health Organization in 2018 [9,10]. This crisis urgently requires an effective and sustainable solution.

A number of therapeutic options have been suggested to control and prevent metabolic disorders. One of the most effective treatments is lifestyle modification for the long term management of body weight and prevention of other metabolic diseases. Yet, it is very difficult to achieve and maintain positive lifestyle interventions [11]. Another option, bariatric surgery, is preferred by some obese patients with a body mass index (BMI) $\geq$ 40 kg/m^2 or type 2 diabetes (T2D) patients with a BMI $\geq$ 35 kg/m^2 [12]. However, massive and rapid weight loss can lead to osteoporosis and malnutrition without actually addressing the root of such diseases [11]. Patients with metabolic disorders can receive drug therapy, such as metformin to treat T2D, however, those allergic to drug ingredients

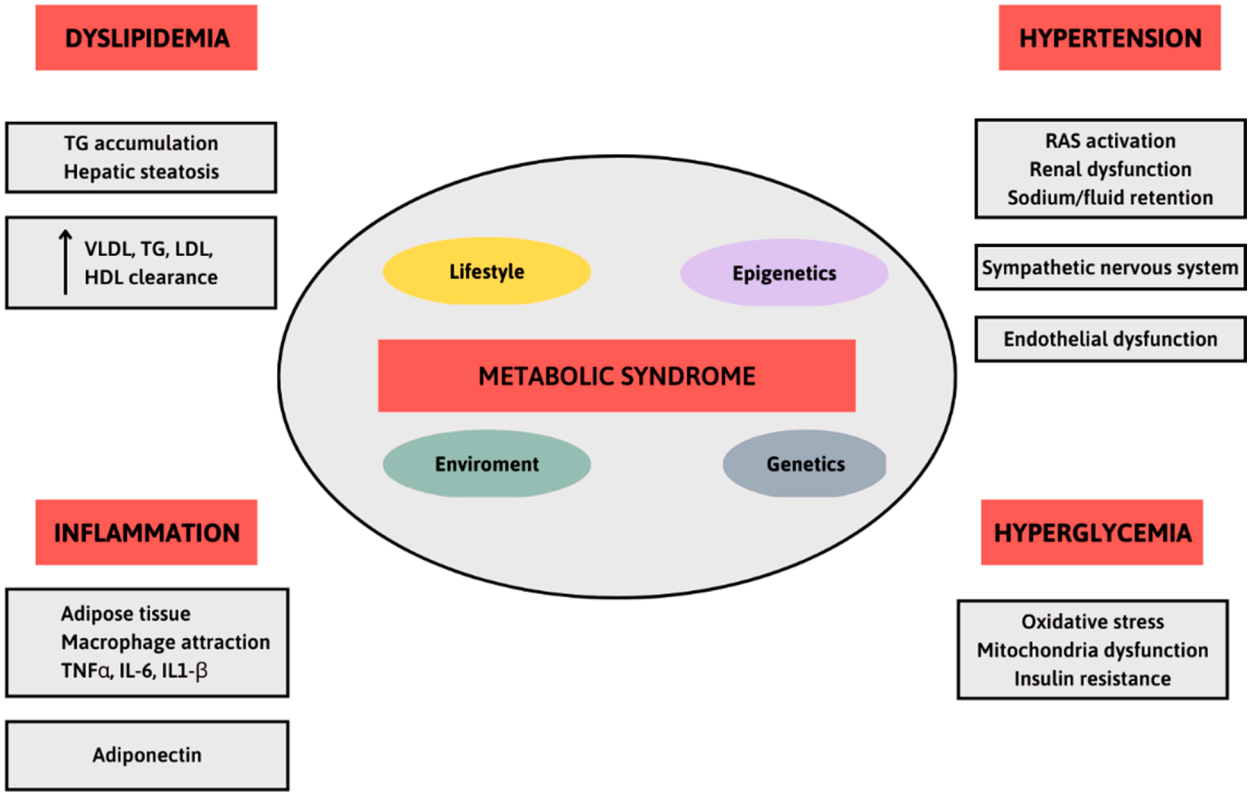

Fig. 1. Causative factors of metabolic disorders. Risk factors of metabolic syndrome are widely known to be genetics, epigenetics, lifestyle and environment. Meanwhile, the pathogenesis of metabolic syndrome still has remained to be fully unexplainable so far but it is considered to be associated with inflammation, dyslipidemia, hyperglycemia and hypertension.

or have severe renal diseases may be unable to seek benefit of it. Certain conditions such as mitochondrial disorders are even more complex due to their considerable influence on all body tissues [13]. As a result, current therapeutic methods for mitochondria dysfunction-related conditions such as Parkinson's, Alzheimer's, and muscular dystrophy are still in the process of being developed and clinically applied [14–18].

One of the most promising therapeutic options could be nanotechnology. This high-potential technology has aroused growing interest due to its considerable influence on many fields, including biology, chemistry, engineering, and medicine. Nanotechnology involves designing and applying materials on the nanometer scale [19]. Nanoparticles exist in the form of small-sized nanospheres [20, 21] with exceptional structural, mechanical, biological, chemical, and magnetic properties that can be utilized to enhance drug quality and drug delivery systems [22,23]. The emergence of nanomedicine is marked by the discovery of the first liposome structure in 1964 [24]. In 1976, the first nanopolymer drug delivery system was documented [25], and the first targeted liposomes were applied for therapeutic purposes [26,27]. In the past decade, nanomedicine has attracted significant research attention [19,28–30]. Nanosensors are highly equipped for the rapid and economical diagnosis of infectious diseases such as COVID-19 [28,31]. In treatment, nanoparticles are usually used to carry chemotherapeutic drugs and support the delivery of anticancer drugs [32–34]. For example, nano-product-based chemo photodynamic therapy is an effective strategy to induce pyroptosis [30]. Mousazadeh et al. [29] found that non-viral nanocarriers associated with cyclodextrin-based carbohydrate polymers were efficient for small interfering RNA (siRNA) [35] cancer treatment.

One of the most promising areas that nanoparticle delivery systems can benefit are nucleic acid (DNA and RNA) therapeutics. There has recently been explosive growth in research on nucleic acid nanoparticle-based therapies for the treatment of various diseases [36]. Certain nucleic acid nanoparticle-based treatments have been intensively studied and have undergone clinical trials. Some treatments have been approved in Europe and the US. For example, Onpattro was recently approved for amyloidosis treatment [37]. For metabolic diseases, nanotechnology and especially nucleic acid therapeutics hold great potential due to their high biocompatibility, limited toxicity, versatility and precise targeting [36,38,39]. In this review, we focus on recent studies on the mechanisms and potential applicability of nanotechnology, especially nucleic acid nanoparticles in treating metabolic disorders and explore future opportunities for better treatment and management of diseases.

2. Nanotechnology for metabolic disorders

Individuals with metabolic disorders account for up to 20–30% of the world's population [40]. Metabolic disorders could be an outcome of several conditions, such as insulin resistance, obesity, dyslipidemia, and cardiovascular disease (Fig. 1). Drugs for hypoglycemia, blood pressure, and other indicators such as neutral fat are used to treat these diseases. The downside of these treatments is that some side effects cause bloating in patients and reduce their ability to tolerate drugs [41]. Nanotechnology is a promising method due to its superior biological distribution, stability, and ability to increase solubilty of natural compounds [33] (Fig. 2).

The cause of diabetes is predominantly due to disregulated secretion or activity of insulin [42]. Diabetes could fall into two categories: Type I (cellular dysfunction leading to insulin deficiency-insulin dependence) and type II (without insulin sensitivity) [43]. The most widely used drug to treat T2D is metformin [44]. Thymoquinone found in *Nigella Sativa* (*Lamiaceae* family) is effective against diabetes and respiratory diseases, especially coronary artery disease [45]. These activities of thymoquinone has been proven *in vivo* and *in vitro*, but has so far not qualified for clinical trials. Using the nanoprecipitation method, Rani et al. created polymeric nanocapsules of thymoquinone and metformin in 2018 and used the formulation on diabetic rats for 21 consecutive days . The results of the study showed that in mice with T2D, the administration of the nanocapsules had a better hypoglycemic effect than biologically active thymoquinone alone [46].

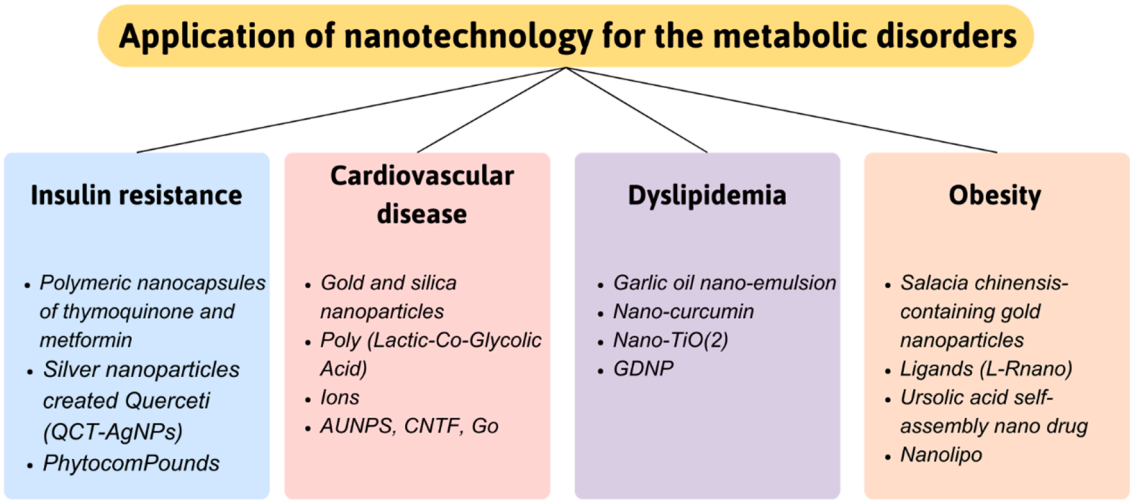

Fig. 2. The applications of various kind of nanotechnologies for treating the metabolic disorders.

This study facilitated further evaluation of anti-hyperglycemic activity *in vivo*. Diabetes has many severe consequences for patients, and one of the most serious consequences is amputation, accounting for 15% of cases. The leading cause of amputation is wounds and foot ulcers caused by diabetes. Nanotechnology is now being applied to diabetes with the advantage of allowing for control of the distribution of stable and specific bioactive compounds at a designated site by preparing hydrogels with silver nanoparticle created Querceti (QCT-AgNPs) for treating diabetic and burn wounds. With this method, the performance and surface morphology could be enhanced. *In vivo* results showed that QCT-AgNP hydrogel enhanced epithelial regeneration when treating diabetic wounds [47]. In addition, some other applications have been found to be effective in treatment or prevention, such as nano delivery systems of phytocompounds [48].

Obesity is currently the most common disease in the world and is also the cause of many diseases related to metabolic disorders. Treatment of obesity through nanosystems, specifically by using *Salacia chinensis*-containing gold nanoparticles (SC-AuNPs) has been applied to evaluate related parameters in obese mice. Once SC-AuNPs are formed, they are further processed using different techniques to optimize their efficiency. In one study, mice showed a reduction in body weight, leptin index, and fat. In addition, this treatment increased high-density lipoprotein and activated protein kinase [49]. The enhanced digestion of the thermogenic energy of white adipose tissue is one of the methods used to correct imbalances in energy metabolism and specific problems related to excess body weight. Despite the advantages gained by this method, there are still certain limitations. To mitigate these limitations, Zu et al. [50] researched the application of resveratrol-loaded nanoparticles to form ligands (L-Rnano). The results of L-Rnano injections in obese mice reduced fat intake by up to 40% in addition to reduced injection status and increased glucose hemostasis. Studies on nir fluorescent dye loaded in the ursolic acid self-assembly nano-drug, nano lipo, have been conducted and applied to nanotechnologies for obesity [51].

Dyslipidemia is a metabolic disorder that occurs due to abnormal changes in the composition of lipids such as triglycerides, cholesterol, low-density lipoprotein, and high-density lipoprotein [52]. Current medications for dyslipidemia include atorvastatin, pravastatin, lovastatin, and simvastatin. However, these drugs can cause side effects such as myalgia, rhabdomyolysis, and many others [53–55]. Studies and applications related to nano-curcumin [56], nano-TiO(2) [54], and ginger-extracted nanoparticles (GDNP) [57] have also been carried out to evaluate nanotechnology in the treatment and diagnosis of dyslipidemia.

A reduction in nitric oxide production (NO) increases the development of cardiovascular risk factors such as increased cholesterol and hypertension. This is the first step of atherosclerosis. Gold and silica nanoparticles have been used to improve the enhanced production of NO. Applying a 17-βe loaded CREKA peptide-modified nanoemulsion system reduces plasma lipid levels and inflammation. Transporting drugs via liposome is effective in preventing platelet capacitors and thrombosis. This method is effective for commonly used blood solubility drugs with new nano therapy to select the congestion locations through mechanical activation [58]. Other studies on nanotechnology such as poly lactic-co-glycolic acid (PLGA), iron oxide nanoparticles (IOs), nanoscale gold particles (AuNPs), carbon nanotube fibers (CNTF), and graphene oxide (GO) have been implemented to determine the application of nanotechnology for cardiovascular disease [59].

The evidence has demonstrated that nanotechnology has great potential applications in managing and improving metabolic disorders. In addition, nanotechnology has provided a progressive foundation for developing new nanomaterials to improve the accuracy, convenience, and safety of the diagnosis and treatment of patients [60].

3. Nucleic acid nanoparticles for metabolic disorders

Nanotechnology is a versatile tool for multidisciplinary research fields and various therapeutic purposes. In particular, nucleic acid-mediated nanomaterial technology provides exclusive control over size, shape, time, anisotropy, and mechanics. It can transfect different types of cells and tissues without any toxic effect, diminish induced immune response, and penetrate most biological barriers [61]. Metabolic skeletal disorders occur due to inflammation and impaired bone formation, and they remain a key clinical challenge. Early therapeutic strategies (antiosteoclastogenic therapy and proosteoblastogenic therapy) were not very effective in treating metabolic skeletal disorders such as osteoporosis [62]. In the pathogenesis of osteoporosis, complex molecular networks of bone and immune factors are responsible. To treat such complex diseases, combined therapeutics are required rather than monotherapy [63]. In the treatment of metabolic skeletal disorders, microRNA-based gene therapy offers numerous therapeutic advantages. Recently, Li et al. [64] performed *in vitro* and *in vivo* studies for metabolic skeletal disorders and used salicylic acid-based nanomedicine with self-immunomodulatory activity to enable microRNA therapy. *In vitro* studies showed that miR-21@PSA-NP with low toxicity could effectively realize the intracellular delivery of miR-21. However, in osteoporotic mice, the outcomes showed that miR-21@PSA-NP-DSS6 enhanced bone accumulation, prolonged blood circulation time, and greatly enhanced the effectiveness of miR-21-based bone anabolic therapy.

Other metabolic disorders, such as liver fibrosis, is one of the leading causes of liver-related morbidity and mortality. Currently, there is no US Food and Drug Administration (FDA)-approved antifibrotic therapy available. To treat liver fibrosis, polymeric nanoparticles have been used. Nanoformulation containing ketal cross-linked nano hydrogel and Cy5-labelled anti-col1a1 (collagen type I alpha 1) siRNA was administered and significantly inhibited fibrosis [65]. Superparamagnetic iron oxide (SPIO)-loaded nanoplex T-PBP@miRNA/SPIO (T-miRNA/S) was utilized. The T-PBP micelle competently transported the miRNA-29b and miRNA-122 to the hepatic stellate cells (HSC), and it significantly downregulated the expression of liver fibrosis-related genes, including α-smooth muscle actin, collagen type I alpha 1, and tissue inhibitor of metalloproteinase 1. The study suggests that combination therapy with miRNA-29b and 122 could be effective in improving liver function and reducing hepatic fibrosis. A more comprehensive and similar approach should be used for other metabolic disorders.

Nucleic acid-based therapy holds great potential for the treatment of some metabolic diseases. However, this approach has suffered

from the least amount of clinical success due to challenges with the delivery method [61,66]. In the last few years, many state-of-the-art nanotechnological techniques have been typically implemented: Nanotechnology is used to deliver certain therapeutic nucleic acids (TNAs) (TNAs with nanoparticle formulation) using carriers such as ASN ODN (ASN = anti-sense; ODN = oligodeoxyribonucleotide), catalytic oligos (DNAzyme - RNAzyme), TFOs (triplex-forming oligonucleotides), IMOs (immunomodulatory oligonucleotides) or for programming and folding nucleic acids into different geometries (Nano-TNA) [67], and some are under development. Typically, the application of nucleic acid nano drugs for phase II/III clinical trials for the purpose of cell reprogramming are being developed [68]. Among these methods, the exosome delivery system is preferred due to its effective cell communication. Due to various concerns, there is a need to advance this approach due to its unique properties, such as low immunity, innate stability and high rates of tissue/cell penetration [69,70].

Furthermore, compared to traditional drug formulations, synthetic nanoparticle-based drug delivery systems are costly and have higher immunotoxicity effects. However, such problems can be avoided by using plant-derived nanoparticles [71]. Recently, Kumar et al. [72] utilized ginger-derived nanoparticles (GDNPs) in theranostics, which have tissue-specific targeting properties as well as greater stability in the gastrointestinal system in addition to presenting colon-targeted delivery and high intestinal epithelium permeability. In their work, miR-375 or antisense-miR375 was filled into nanoparticles made from lipids extracted from GDNP. *In vivo* GDNPs were used in mice, and it was demonstrated that GDNPs can help protect mice from alcohol-induced liver damage [73] and inflammatory bowel disease [74]. They also presented high anti-inflammatory efficacy in mouse models of colitis [75] and in a mouse model of high fat diet (HFD)-induced type 2 diabetes mellitus (T2DM) [72]. Understanding deregulated microRNAs could be an innovative approach to tackling many metabolic disorders. The combination of different miRNAs could lead the way to more effective personalized treatments.

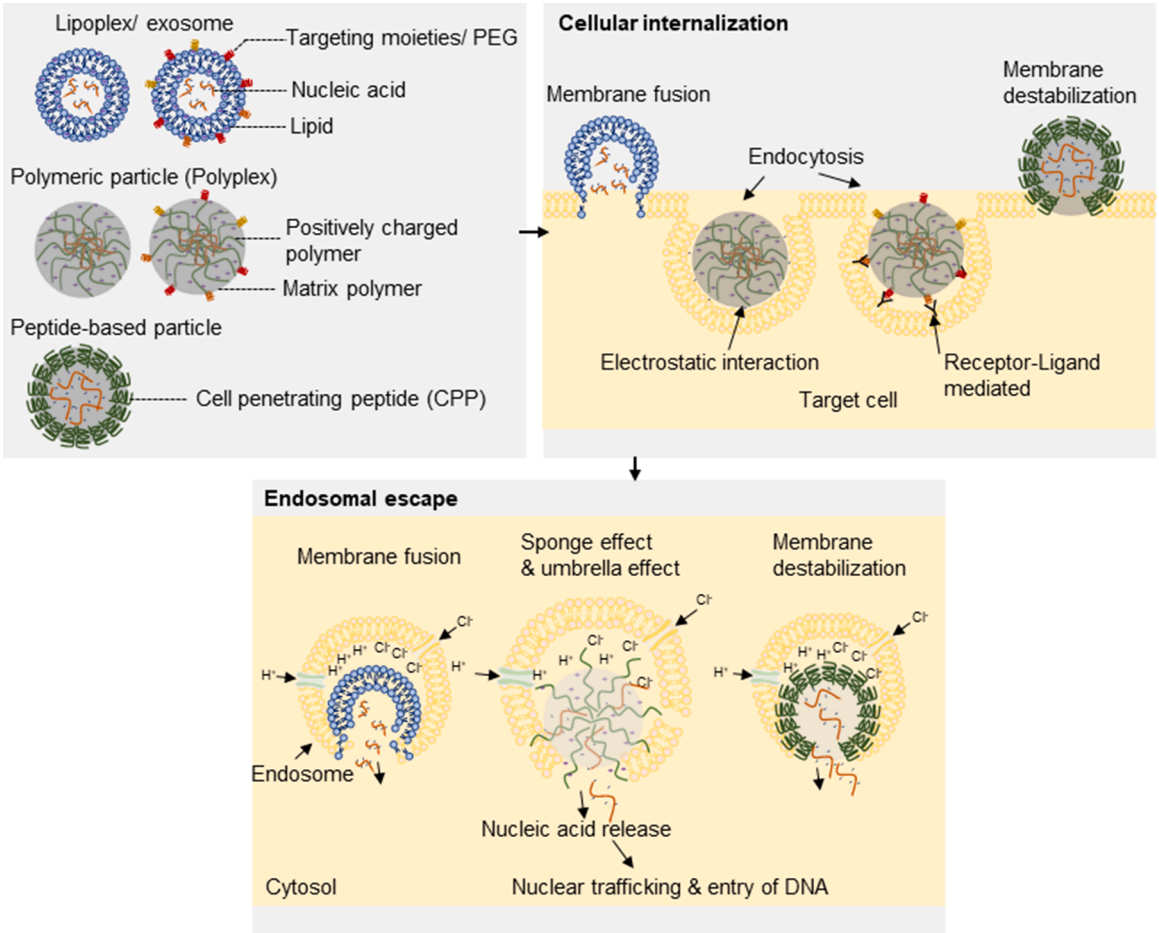

Fig. 3. Mechanism of nucleic acid nanoparticle delivery in the treatment of metabolic disorders. Nucleic acid nanoparticles, including lipoplex/ exosome, polyplex, and peptide-based particles, could protect and enhance the retention time of therapeutic nucleic acids in the body after administration, and efficiently deliver them to target cells. In these cells, nanoparticles undergo cellular internalization via various pathways (membrane fusion, passive and active endocytosis, and membrane destabilization), and subsequent endosomal escape to release nucleic acids via membrane fusion, sponge & umbrella effects, and membrane destabilization. Exogenous DNA materials further reach and enter nuclear by active and passive pathways. The detailed mechanisms of each therapeutic nucleic acid in cells can be seen in the previous review [66].

4. Mechanisms of nanotechnology and nucleic acid nanoparticles for metabolic disorders

Nanotechnologies have been extensively applied in the management and treatment of metabolic disorders. Nanotechnologies include using nano-sized drugs and drug depots to enhance retention in the body and target diseased sites, thereby improving the therapeutic efficacy of drugs while reducing their side effects [76,77]. In oral delivery systems, nanoparticles have been used to protect drugs from pH and enzyme degradation in the gastrointestinal tract, to improve contact and residence time in the intestinal epithelium, and to escape first-pass metabolism in the liver via lymphatic uptake [78]. Polymeric nanoparticles (e.g., PLGA) are frequently utilized to prolong drug release time, possibly reducing the dosing frequency [79,80]. Lipid-based nanoparticles, including liposomes and exosomes, are cell-friendly and easily up taken by cells, which improves drug delivery efficiencies [81]. In addition, PEGylation (surface functionalization with polyethylene glycol) of nanoparticles reduces the immunogenicity and phagocytosis and enables prolonging their systemic circulation time [78,82–84]. In advanced nanotechnologies, nanoparticles are functionalized with bioactive targeting moieties (e.g., N-acetylgalactosamine (GalNAc), antibodies), aiming to actively target diseased sites with higher efficiencies than traditional approaches [85–88].

Nucleic acid therapeutics mainly involve the use of messenger RNA (mRNA), siRNA, microRNA (miRNA), antisense oligonucleotides (ASOs), and plasmid DNA (pDNA) [35,66]. Many of them are extremely unstable and immunogenic, hampering the application of nucleic acid therapy. Using nanotechnologies, various nanoscale nucleic acid therapeutics have been developed to treat metabolic disorders. These particles protect nucleic acids from premature enzymatic degradation and immune responses, as well as facilitate their uptake into the target host tissues/cells. In the cells, they undergo cytosolic degradation to release DNAs/RNAs to promote (in DNA and mRNA delivery) or inhibit (in siRNA and miRNA delivery) encoded protein production.

The physicochemical properties of carriers govern their internalization, intracellular process, and release of delivered nucleic acids (Fig. 3) [89]. Lipoplexes and exosomes contain unique synthetic or natural lipid molecule carriers and can internalize the cells via both direct cell membrane fusion and endocytosis [90], whereas polymeric particles mostly utilize endocytosis [89]. The functional molecules on nanoparticles determine the internalization pathways; for example, clathrin-mediated endocytosis by transferrin conjugation and caveolar-mediated endocytosis by folic acid conjugation [91]. Some peptides, which can insert and destabilize cell membranes, have been utilized to deliver therapeutic nucleic acids in metabolic disorders [92]. After cellular internalization, nanoparticles are located in the endosome-lysosome system and the mechanisms by which they undergo the endosomal escape process under prompt pH drop by the lysosome and determine the efficiency of gene therapy. In lipoplex, nucleic acids can be released via the fusion of lipid carriers with the endosome membrane and the swelling of the endosome due to increased osmotic pressure by the sponge effect of pH-sensitive lipids (i.e., DOSPA) [93,94]. Polymeric particles, containing positive-charged polymers, escape from the endosome-lysosome system via the sponge effect and umbrella effect (the expansion/protonation of polymers at low pH) [95,96]. Peptide-functionalized nanoparticles exhibit an endosomal escape via various mechanisms, including the sponge effect, fusogenic effect, and membrane destabilization. In the next step, functional nucleic acids need to be released from the carriers and target cytoplasmic machinery to achieve their effect. Destabilization of the nucleic acid-carrier can be via the membrane fusion process in

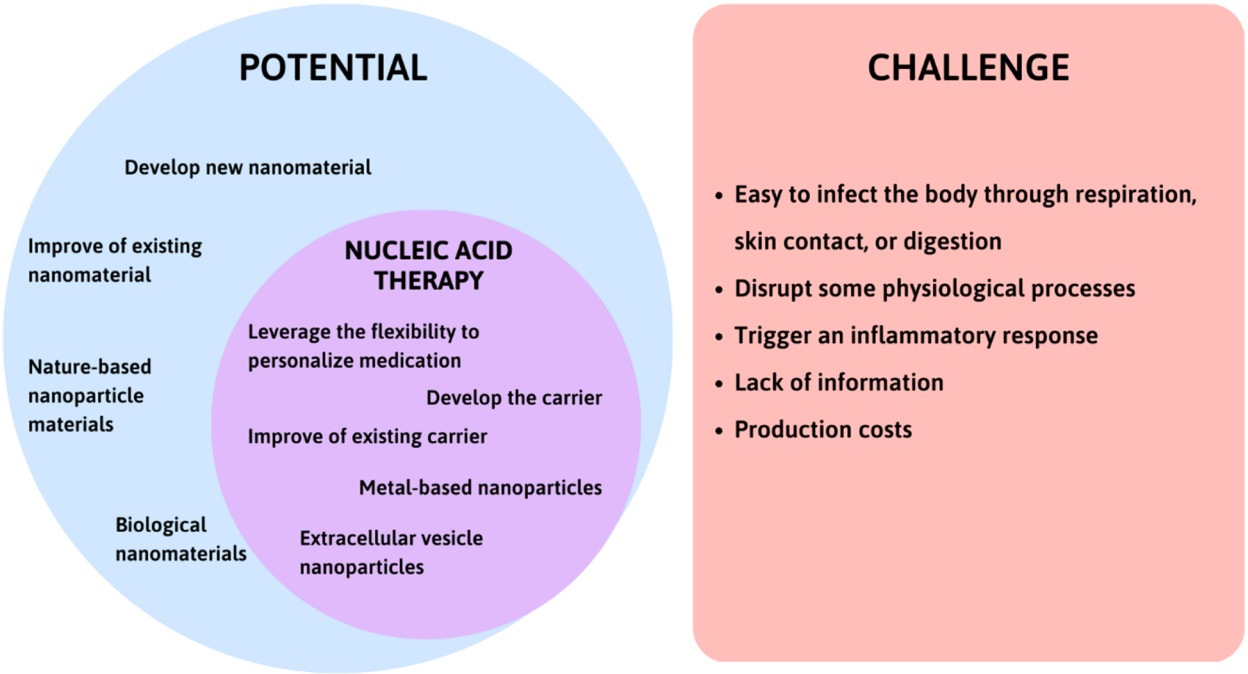

Fig. 4. The potentials and challenges of nanotechnology.

lipoplex formulation, or via anionic exchange of nucleic acids in polymeric particles [89]. In the case of DNA delivery, active nuclear trafficking through microtubules occurs with nuclear entry through passive and active pathways [89]. In summary, the transfection efficiency of exogenous nucleic acids is affected by the types and characteristics of carriers via modulating the specific mechanisms of how nucleic acids are protected and processed until they resemble cytoplasmic machinery for protein translation.

5. The potential applications of nanotechnology and nucleic acid nanoparticles for metabolic disorders

The current treatment of metabolic disorders is challenging due to its pathophysiological complexity [97]. This review article has attempted to address the question of potential applications in nanotechnologies and nucleic acid nanoparticles for combating metabolic disorders. The potential application of nanotechnologies mainly comes from developing and optimizing nanomaterials [98,99], in which nature-based nanoparticle materials have also been seen as promising applications in the future. These have many advantages, such as high biocompatibility, limiting the possibility of toxicity and side effects [100]. In addition, the use of natural nanomaterials minimizes the possibility of accidental exposure compared to artificial materials [101]. This has proven to be a new research direction that has attracted scientists is the development of biological nanomaterials. The advantages include high biocompatibility and less toxicity than chemically synthesized nanomaterials [102]. Therefore, the use of drugs containing biological nanomaterials has been evaluated as future therapies in the treatment of metabolic disorders. Fig. 4 depicts the potentials and challenges of nanotechnology.

Nucleic acid therapy is rapidly emerging and has been considered as one of the most promising areas in metabolic disorder treatment. The main advantage of nucleic acid drugs lies in precisely targeting the desired tissues and cells and then releasing the therapeutic proteins or biological substances at that site . Another advantage is its versatility. New drugs can be easily created or existing ones improved just by changing the nucleotide sequence of the target gene [103]. Interestingly, this advantage can be harnessed due to the advancement of gene sequencing technology. Thus, this therapy has great applicability if scientists fully exploit its potential, especially personalized drug development in metabolic disorder treatment. Moreover, nucleic acid therapy works by many different mechanisms, and the transmission efficiency of exogenous nucleic acids is affected by the characteristics of the carrier [104]. Some nanocarriers have been evaluated as having high application potential based on their superior properties such as metal-based nanoparticles [105] and extracellular vesicle nanoparticles [103]. Thus, having greater insight into the potential carriers of this therapy is essential.

Although the application of nanotechnology, especially nucleic acid therapy, is gradually gaining momentum, many challenges remain. The explosion of nanotechnology has led to widespread discussions about the safety and potential health risks. Some evidence has shown that nanoparticles can easily enter the body through respiration, skin contact, or digestion [106]. Thereafter, the nanoparticles are fully capable of moving through the blood-brain barrier due to their high mobility. Moreover, nanoparticles can disrupt some of the body's physiological processes and trigger an inflammatory response [58]. On the other hand, information on the physicochemical properties of nanoscale systems in metabolic disorders as well as the expected toxicity remains unclear. In particular, production costs are another obstacle [107]. To this day, no nano drugs for metabolic disorders have been licensed. Nanodrugs have been used most successfully in cancer treatment [108]. Therefore, the application of nanotechnology to metabolic disorders can refer to cancer treatment strategies because there are some similar pathological features between them [51]. In the long run, further studies are necessary to fully leverage the potential of this technology in the diagnosis and treatment of metabolic disorders in humans.

6. Conclusions and future remarks

Metabolic disorders are now the major clinical challenge of global health. Common metabolic syndromes include obesity, insulin resistance, atherosclerosis, and systemic blood pressure disorders. They involve the inborn and acquired dysfunction of organs and tissues that are responsible for producing energy for the body. Nanotechnology has been seen as a potential application in biomedicine, especially to defeat metabolic syndrome and related disorders. The evidence for its application in metabolic disorders has been mostly based on interventions in animal models. Diabetes mellitus seems to be the disease that has benefited the most from this technology with applications in glucose measurement and drug delivery. In particular, nucleic acid therapeutics have been a promising area which nanotechnology can benefit. The success of this therapy depends mainly on the characteristics of carriers, via modulating the specific mechanisms of how nucleic acids are protected and processed until they resemble cytoplasmic machinery for protein translation. Given the versatility of nucleic acid therapy, research into personalized drug development is a potential direction. Although this therapy has received special attention in recent times, the safety remains challenging. Nanoparticles can easily enter the body through respiration, skin contact, or digestion. In addition, it can also be toxic or affect the physiological functions of the body. Furthermore, the production cost is another obstacle. In the long run, further studies are integral to fully leverage the potential of this technology. In summary, this review helped shed light on current approaches and the future potential of nanotechnology and nucleic acid therapy in metabolic disorders. We hope that this knowledge will be useful for navigating potential applications in the treatment of these common diseases and contribute to a better quality of global health in the future.

CRediT authorship contribution statement

Dinh-Toi Chu: Conceptualization, Supervision, Writing – review & editing. **Hue Vu Thi:** Writing – review & editing. **Tiep Tien Nguyen:** Writing – review & editing. **Thuy-Duong Vu:** Writing – review & editing. **Yen Vy Nguyen Thi:** Writing – review & editing. **Indra Mani:** Writing – review & editing. **Nisarg Gohil:** Writing – review & editing. **Gargi Bhattacharjee:** Writing – review & editing.

Suresh Ramakrishna: Writing – review & editing. **Vijai Singh:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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