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Therapeutic medications against diabetes: What we have and what we expect

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ABSTRACT

Diabetes has become one of the largest global health and economic burdens, with its increased prevalence and high complication ratio. Stable and satisfactory blood glucose control are vital to reduce diabetes-related complications. Therefore, continuous attempts have been made in antidiabetic drugs, treatment routes, and traditional Chinese medicine to achieve better disease control. New antidiabetic drugs and appropriate combinations of these drugs have increased diabetes control significantly. Besides, novel treatment routes including oral antidiabetic peptide delivery, nanocarrier delivery system, implantable drug delivery system are also pivotal for diabetes control, with its greater efficiency, increased bioavailability, decreased toxicity and reduced dosing frequency. Among these new routes, nanotechnology, artificial pancreas and islet cell implantation have shown great potential in diabetes therapy. Traditional Chinese medicine also offer new options for diabetes treatment. Our paper aim to overview these therapeutic methods for diabetes therapy. Proper combinations of these existing antidiabetic medications and searching for novel routes are both necessary for better diabetes control.

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1. Introduction

Diabetes is a complex, chronic disease characterized by deficient β-cell insulin secretion in the setting of insulin resistance. Currently, diabetes is one of the largest global health threats and is included among the top 3 noncommunicable diseases that account for over 80% of all premature noncommunicable disease-related deaths; furthermore, it is among the top 10 causes of death worldwide. Its global prevalence has rapidly increased over the past several decades. According to the most recent edition of the International Diabetes Federation (IDF) Diabetes Atlas [1], 425 million 20- to 79-year-olds have diabetes (prevalence, 8.8%), and this value increases to 451 million when the age range is expanded to 18- to 99-year-olds. If this trend continues, the numbers of 20- to 79-year-olds and 18- to 99-year-olds with diabetes will each increase to 629 million and 693 million, respectively, by 2045. This large increase in diabetes is the result of population growth, aging, and the economic transition from low to middle income levels. Across IDF regions, the prevalence of diabetes differs by region and country. The age-adjusted comparative prevalence among 20- to 79-year-olds was highest in North America and the Caribbean (11.0%) and lowest in Africa (4.2%) in 2017, most likely because of lower levels of urbanization and obesity as well as higher levels of under-nutrition in Africa. The 3 countries with the largest numbers of people with diabetes in 2017 were China, India and the United States. Moreover, it is estimated that approximately 50% (212.4 million) of adults with diabetes are undiagnosed, and 7.3% (352.1 million) of adults have impaired glucose tolerance. Therefore, it is imperative to screen the high-risk population and provide appropriate recommendations for people with diabetes.

The classification of diabetes is complex, but it is now widely acknowledged that there are three main types of diabetes, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM). Besides, there are also some less common types of diabetes which include monogenic diabetes and secondary diabetes. As the most common type of diabetes, T2DM accounts for around 90% of all cases of diabetes. Patients with T2DM have increased rates of macro- and micro-vascular complications, which contribute to increased premature mortality and lower quality of life for both these patients and their families. Moreover, the control of diabetes remains unsatisfactory. According to the United States National Health and Nutrition Examination Surveys from 2003 to 2006, 58.2% of people achieved their target goals for glycemic control (HbA1c <7%) [2]. In the 3B study, which examined blood glucose, blood pressure, and blood lipids in China [3], only 47.7% of outpatients with diabetes met their goals for HbA1c control (HbA1c <7%). A cross-sectional study in Poland in 2009 revealed that only 28.9% of individuals with diabetes had an HbA1c level of <6.5% [4]. Other countries have also reported less than satisfactory outcomes regarding the control of cardiovascular risk factors among patients with T2DM [5–10]. Unsatisfactory glycemic control contributes to premature disability and death and is also related to increased risks for cancer, cognitive disability and depression [11,12]. For example, people with diabetes are 10 times more likely to have end-stage renal disease and 2 to 3 times more likely to have cardiovascular disease [13–15]. Moreover, approximately 35% of people with diabetes have diabetic retinopathy, which is the leading cause of blindness in the labor force [16]. Importantly, diabetes accounts for approximately 10.7% of global all-cause mortality, which is higher than the rate associated with infectious diseases. Approximately 4.0 million deaths between the ages of 20 and 79 years were attributed to diabetes in 2017 [1].

In addition to the human burden, diabetes also imposes serious economic pressures on countries and their healthcare systems. IDF showed a significant growing healthcare expenditure from 232 billion USD in 2007 to 727 billion USD in 2017 by 20- to 79-year-olds with diabetes. This economic burden is estimated to increase to 776 billion USD by 2045 [1]. Another global economic analysis using epidemiological and demographic data from 180 countries in 2015 also indicated similar global trends, namely, the costs of diabetes are tremendous and will continue to increase through 2030 [17]. These economic effects will not be attenuated even if countries meet the "Sustainable Development Goal".

2. Treatment of diabetes

Antidiabetic drugs are a fundamental strategy for managing T2DM. Current commonly used antidiabetic drugs include the following categories: metformin, sulfonylureas, glinides, thiazolidinediones, α-glucosidase inhibitors, incretin-based agent-like glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and insulin.

Fig. 1 shows target organs and mechanism of different types of antidiabetic drugs except insulin.

2.1. Metformin

As the only type of biguanide approved for the clinical treatment of diabetes [18], metformin remains the first-line treatment, especially for obese patients [19–21]. Metformin is not only used for the glycemic control of patients with T2DM but also to delay or prevent the progression of impaired fasting glucose and impaired glucose tolerance into T2DM [22,23]. The hypoglycemic mechanism of metformin is still not fully understood [24–26]. Metformin is traditionally thought to increase liver insulin sensitivity by reducing hepatic glucose production. Metformin inhibits mitochondrial Complex I, preventing ATP production, thereby increasing AMP/ATP and ADP/ATP ratios, thus activating AMP-activated protein kinase (AMPK), affecting the energy metabolism. Increases in AMP/ATP ratio also inhibit fructose-1,6-bisphosphatase, resulting in the acute inhibition of gluconeogenesis with a AMPK-indpendent way. Besides, there is increasing evidence that metformin can impact on glucose metabolism via actions on gut. Metformin could increase gut glucose utilisation, increase GLP-1 secretion and alter the gut microbiome. According to the UK Prospective Diabetes Study (UKPDS), metformin can reduce glycated hemoglobin by 1%, especially in obese individuals [27]. Metformin not only helps lower the weight of patients but also (and more importantly) significantly reduces T2DM-related mortality and other adverse end points. According to a statement on the clinical use of metformin by the European Association for the Study of Diabetes and the American Diabetes Association, metformin is recommended as the basic treatment for T2DM in combination with diet and exercise [21]. Metformin is also widely used as a

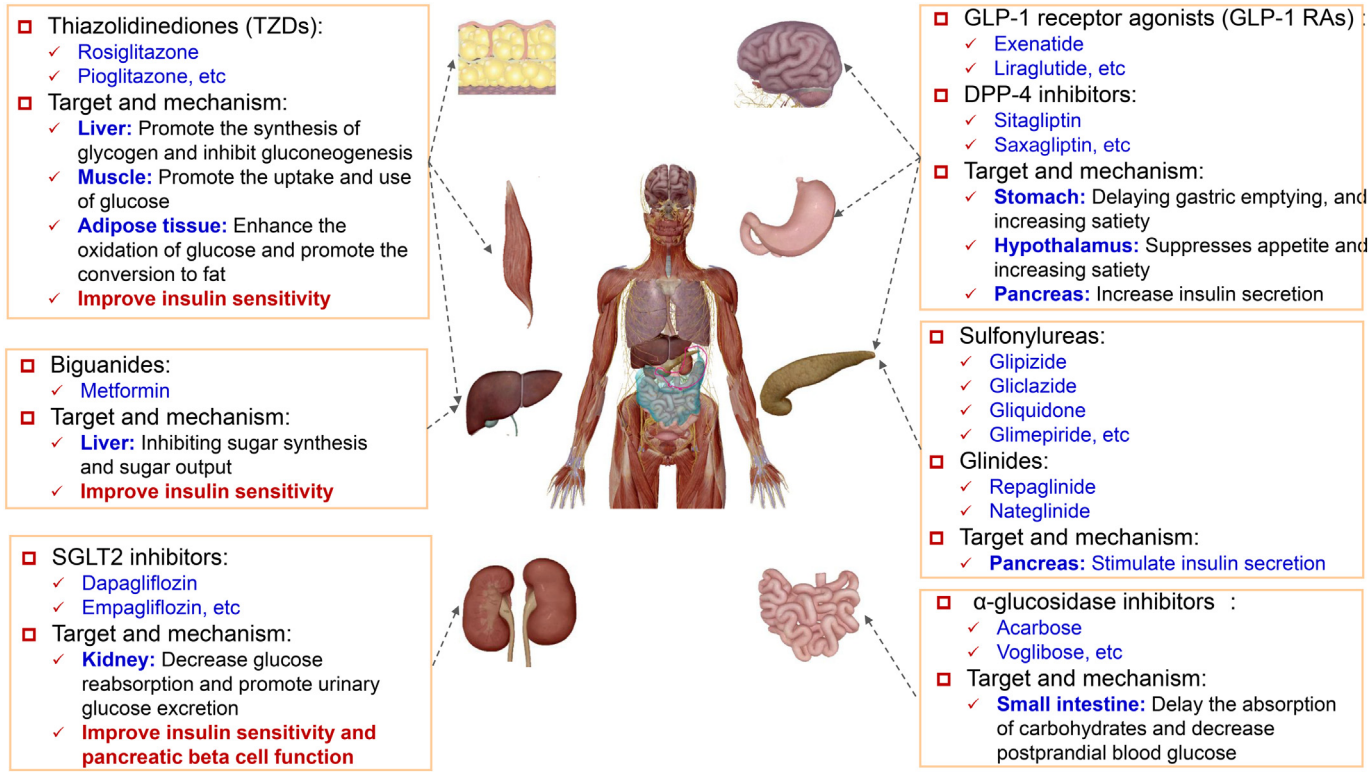

Fig. 1. Target organs and mechanism of different types of antidiabetic drugs. As shown in Fig. 1, eight types of commonly used antidiabetic drugs act on eight targeted organs to improve insulin sensitivity and stimulate insulin secretion, thus to regulate glucose homeostasis. Biguanides, TZDs and SGLT2 inhibitors mainly work on the peripheral tissues including liver, muscle, adipose tissue and kidney, thus to alleviate insulin resistance. Sulfonylureas, Glinides, GLP-1 RAs and SGLT2 inhibitors mainly target on pancreas, stomach, hypothalamus, and kidney, thus to improve beta cell function and stimulate insulin secretion. Finally, α-glucosidase inhibitors mainly works on small intestine, to delay carbohydrates absorption, thus to lower postprandial blood glucose.

part of combinational treatment for T2DM. Numerous clinical trials of antidabetic drugs have used metformin as a basic medication [28–30]. One study found that patients with treatment of empagliflozin and metformin had significantly lower HbA1cl lever and lower risk of hypoglycaemia than those with glimepiride and metformin [29]. Another study found that Dapagliflozin and metformin showed hypoglycemic efficacy similar to that of glimepiride and metformin, with a lower body weight and lower incidence of hypoglycaemia [30]. The most common adverse reactions were gastrointestinal reactions, and more than half of the patients were able to tolerate the maximum dose; however, 5% of the patients were unable to tolerate any dose of metformin [18].

2.2. Sulfonylurea

Sulfonylurea is one type of insulin secretagogue. Its action is mediated by adenosine-triphosphate-dependent potassium channels (K_{ATP}) which consists of two different types of protein subunits: sulfonylurea receptor subunits (SUR1, SUR2A or SUR2B) and inwardly rectifying K^+ (Kir) channel subunits (Kir6.1 or Kir6.2) [31,32]. Human different tissues have various combinations of these subunits. SUR1 and Kir6.2 are predominantly expressed in pancreatic β-cells. Binding to SUR1 in the pancreatic β-cell, sulphonylureas can inhibit K_{ATP} channels, resulting in the depolarization of the β-cell membrane, then lead to opening of voltage-dependent Ca^{2+} channels, resulting in intracellular Ca^{2+} influx which stimulates the secretion of insulin in β-cells. Sulfonylurea drugs primarily include two generations. First-generation agents include tolbutamide, tolacarburea, chlorpropamide, and hexahydrourea acetate, and second-generation agents include glibenazide, glipizide, glizide, and glimetazide. Compared with first-generation drugs, second-generation drugs have stronger effects, longer action durations, and fewer adverse reactions. The most common adverse reaction to sulfonylureas is hypoglycemia, followed by weight gain [33]. Hypoglycemia is commonly observed in patients taking long-acting sulfonylurea agents (e.g., glibenclamide).

2.3. Glinides

Glinides, including repaglinide, nateglinide and mitiglinide, are a type of fasting insulin secretagogue that can help mimic early-phase insulin release, thereby providing improved control of postprandial glucose [34]. Compared with sulfonylureas, glinides displayed a faster and briefer insulinotropic activity through binding to its distinct sites on the pancreatic β-cell membrane [35]. Clinical trials have proven that as a monotherapy, glinides could decrease HbA1c levels effectively in patients with T2DM [36], as well as in combination therapy [37]. Compared with gliclazide (30 mg, once daily), repaglinide (1 mg, three times daily) can more significantly increase the insulin levels in patients 30 min after a standard meal [38]. Clinical trials have shown that repaglinide combined with lifestyle interventions can significantly reduce HbA1c levels; furthermore, the incidence of hypoglycemia is rare [39]. Because of its fast and brief insulinotropic action, glinides mainly reduce postprandial glycemia, and proper diet and exercise are also important to maintain long-term glycemic control at the same time.

2.4. Thiazolidinediones

Thiazolidinediones (TZDs) are insulin-sensitizing agents that act as agonists of the nuclear factor peroxisome proliferator-activated receptor-γ (PPAR-γ), thereby leading to improvements in insulin sensitivity, especially in the peripheral tissues. TZDs can promote the synthesis of glycogen and inhibit gluconeogenesis in the liver. Moreover, they can enhance the oxidation of glucose and promote the conversion to fat in adipose tissue [40]. TZDs can also promote the uptake and use of glucose in skeletal muscle. Their insulin-sensitizing effect is not only found

in diabetic conditions but also in certain non-diabetic conditions such as obesity [41]. TZDs include rosiglitazone, pioglitazone, and troglitazone. Troglitazone has been banned for clinical use because of its hepatotoxicity. Rosiglitazone and pioglitazone are the most commonly used agents. In clinical trials, TZDs have reduced the HbA1c levels of patients with T2DM by 0.5–1.4% [42]. According to a diabetes outcome progression trial (ADOPT) study, rosiglitazone showed the strongest ability to control blood glucose in newly diagnosed patients with T2DM compared with glyburide and metformin [43]. In addition, TZDs can also inhibit islet β-cell apoptosis and protect β-cell function, thereby effectively delaying the course of diabetes in animal models [44]. Although TZDs have excellent hypoglycemic effects and lipid regulation, controversy exists regarding their application because of their effect on the risk of cardiovascular events [45]. However, recent prospective studies have confirmed that no evidence suggests that rosiglitazone increases the risk of cardiovascular events; rather, data have highlighted its hypoglycemic benefits [46,47].

2.5. GLP-1 RAs and DPP-4 inhibitors

The hormone incretin plays an important role in glucose homeostasis. GLP-1 is secreted by the L cells of the gut in response to food ingestion. Incretin mediates the effects of decreased glucose by increasing glucose-dependent insulin secretion, decreasing glucagon secretion, delaying gastric emptying, and increasing satiety [48,49]. GLP-1 receptor agonists (GLP-1 RAs) are synthetical analogs of GLP-1 through modifying pharmacokinetic properties over native peptides [50]. Currently, there are 6 GLP-1 RAs approved for the treatment of T2DM, including twice-daily exenatide, once-daily liraglutide, lixisenatide, once-weekly extended-release exenatide, dulaglutid, albiglutide,and semaglutide [51,52]. The endogenous GLP-1 can be rapidly degraded by the DPP-4 enzyme. DPP-4 inhibitors augment endogenous GLP-1 by preventing its degradation, thereby playing the role of hypoglycemic [53]. DPP-4 inhibitors include sitagliptin, saxagliptin and linagliptin. Clinical trials have shown that GLP-1 RAs and DPP-4 inhibitors significantly reduce fasting and postprandial hyperglycemia, as well as HbA1c. GLP-1 RAs can decrease HbA1c by 0.3% to 1.9% [51], whereas DPP-4 inhibitors reduced HbA1c by 0.6% to 1.1% [54]. Both GLP-1 RAs and DPP-4 inhibitors display satisfactory safety, tolerability, and low risk of hypoglycemia owing to their glucose-dependent mechanism of action [55,56]. The most frequently reported adverse effects of GLP-1 RAs are gastrointestinal disorders that tend to be relieved as treatment proceeds [57], and nasopharyngitis is the most frequently reported adverse event associated with DPP-4 inhibitors. Regarding the effects of these two types of drugs on cardiovascular outcomes, a recent meta-analysis showed that GLP-1 agonists are associated with a lower mortality rate than DPP-4 inhibitors or placebo. However, the use of DPP-4 inhibitors was not associated with a lower mortality rate than placebo or no treatment [58].

2.6. SGLT2 inhibitors

SGLT2 inhibitors reduce hyperglycemia by promoting glucose excretion from kidney. SGLT is a family of glucose transporters including SGLT1 and SGLT2 that are critical for glucose homeostasis. SGLT2 is specifically expressed on the proximal renal tubules and responsible for the transport of D-glucose [59]. It is responsible for 90% of the glucose reabsorption of the original urine [60]. In patients with diabetes, the SGLT2 in the proximal tubule is over-expressed, and glucose reabsorption is increased, resulting in elevated blood glucose [61,62]. SGLT2 inhibitors reduce 30% to 50% glucose reabsorption and thus yield hypoglycemic effect [63]. In addition to the hypoglycemic effect, SGLT2 inhibition also causes a series of pathophysiological changes. SGLT2 inhibition can improve insulin resistance and islet beta cell function [64,65], increase plasma glucagon levels [66], and improve glomerular hyperfiltration during the early stage of diabetic kidney disease [67,68]. According to previous clinical trials, whether used as a monotherapy or in combination with other hypoglycemic agents, SGLT2 inhibitors can significantly improve blood glucose [69], control blood pressure [70], and reduce weight [71]. The famous clinical trial Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose (EMPA-REG OUTCOME) [72,73] evaluated the influence of SGLT2 inhibitors on cardiovascular outcomes. In that trial, patient treated with empagliflozin had lower risk of adverse cardiovascular events, hospitalization and mortality, compared with those treated with placebo. The main adverse effects of SGLT2 inhibitors are urinary tract infection and genital infection. The other rare adverse effects include postural dizziness, orthostatic hypotension, urinary calcium excretion increase, fracture, and ketoacidosis [74,75].Nevertheless, SGLT2 inhibitors were well tolerated in those trials.

2.7. Insulin

Insulin therapy is a life-saving treatment of controlling hyperglycemia for diabetes mellitus [76]. Patients suffered from type 1 diabetes mellitus are insulin-dependent [77] and the risks of diabetic macrovascular and microvascular complications could be reduced by insulin [78]. For type 2 diabetes patients with contraindications to oral antidiabetic agents, or the blood glucose levels do not meet the control target after combination therapy of lifestyle interventions and oral hypoglycemic agents, the treatment of insulin can be started [79,80]. For those individuals with long course of diabetes mellitus, insulin therapy could become indispensable parts of glucose homeostasis measures. The recent 100 years have witnessed the pattern of development from the discovery of insulin to the commercial application of insulin preparations and its analogues [81]. Generally, there are three major sources of insulin preparations based on different production techniques: animal insulin, human insulin and insulin analogues. According to the different roles of its action, insulin preparations are further divided into three categories: rapid-acting insulins (insulin analogues), long-acting insulins (insulin analogues) and pre-mixed insulins (insulin analogues) [82]. Rapid-acting insulins are mainly used for the management of mealtime blood glucose, while long-acting insulins for daily basal insulin needs [83]. In view of the inconveniences occurred in the subcutaneous insulin injections, attempts have been made in the past decades in the application of the insulin pumps of continuous infusion [84]. Of utmost important advance is the closed-loop automated insulin delivery system [85]. It is worth noting that, compared to oral drugs, insulin therapy requires more collaborations between medical staffs and patients, and more glucose self-monitoring skills for patients [86]. Further attentions should be paid to strengthen blood glucose monitoring and insulin adjustment to avoid hypoglycemia [87].

3. Promising therapeutic routes for patients with diabetes

Ideal diabetes treatments should be safe, efficient, convenient and economical with an assurance of patient compliance. Therefore, innovations in the administration route of drugs are meaningful for diabetes therapy to achieve better disease control. Here, we primarily focus on the new therapeutic routes for diabetes.

3.1. Oral antidiabetic peptide delivery

Based on the mechanism of diabetes, oral antidiabetic peptide delivery primarily focuses on improving insulin resistance, promoting insulin secretion or adding insulin directly via subcutaneous, pulmonary, nasal, transdermal or oral routes [88]. Among the various routes of administration, the oral route is often the most preferred due to its convenience, high comfort degree and low potential cost. Furthermore, oral insulin can achieve rapid hepatic insulinization without peripheral hyperinsulinemia, thus reduces the possibility of hypoglycemia and weight gain [89,90]. GLP-1 is an incretin peptide secreted by the

neuroendocrine L cells of the ileum and colon [91]. Oral GLP-1 and its analogs can mimic the the natural physiological route of GLP-1 and reduces the number of potential side effects [92]. Therefore, the oral administration route is an important diabetic therapeutic intervention that affects both the pharmacokinetics and the efficacy of the drug.

However, not all medicines can be taken orally, especially proteins and peptides with structures that are pivotal to their function. Due to the degradation caused by proteolytic enzymes and absorption barrier from the digestive tract, antidiabetic peptides, such as insulin and GLP-1 RAs, remain administered via subcutaneous injection. Furthermore, patient compliance is influenced by the pain or discomfort of injection, the risk of infection and psychological stress [93]. The oral route of antidiabetic peptides is pivotal to reduce the morbidity and mortality related to hyperuricemia considering its possible effective action, low toxicity, and greater acceptability to patients. Many studies are motivated to find solutions for the delivery of antidiabetic peptides via the oral route.

Currently, antidiabetic peptides cannot be taken orally because of two major obstacles: the first obstacle is digestive destruction from gastric acid and proteolytic enzymes, and the second is the absorption barrier from the intestinal mucosa, epithelial cells and hepatic first-pass effect [94]. Many techniques have been developed to overcome the obstacles associated with oral antidiabetic peptides, and challenges are also present with regard to their development.

Fig. 2 shows a summary of different oral antidiabetic peptide delivery.

3.1.1. Overcoming digestive destruction

Because the gastrointestinal tract is the main organ in which oral antidiabetic peptides are digested via gastric acid and other proteolytic enzymes, the first challenge in achieving the pharmacological action of oral insulin, GLP-1 or its analogs is to retain the complete biological structure of these peptides in the gastrointestinal tract. Therefore, researchers have made efforts to protect the peptides from digestion by these gastric and intestinal enzymes via modifying their structure, using enzyme inhibitors, or both.

Like other proteins or peptides, insulin, GLP-1 RAs have unique molecular structures and markers through which they can be recognized by exact receptors or degraded by specific enzymes. Therefore, many chemical modification strategies for the oral peptides have been studied to protect drugs from digestion, for instance, cyclization, lipidation, PEGylation and biotinylation. These strategies offer great potential for oral peptides.

Among these modification methods, PEGylation is an old but promising method with regard to oral insulin. PEG polymers are mixtures of polymers that can be attached to protein or polypeptide drugs covalently. Through PEGylation, the structure of insulin can be modified and will not be recognized or degraded by proteolytic enzymes in the gastrointestinal tract; therefore, its stability can be maintained. PEGylation increases the stability and potency of insulin [95], thereby enhancing the bioavailability and enzyme resistance of oral insulin and extending the duration of the hypoglycemic effect [96]. Furthermore, combining PEGylation with nanotechnology can sustain the

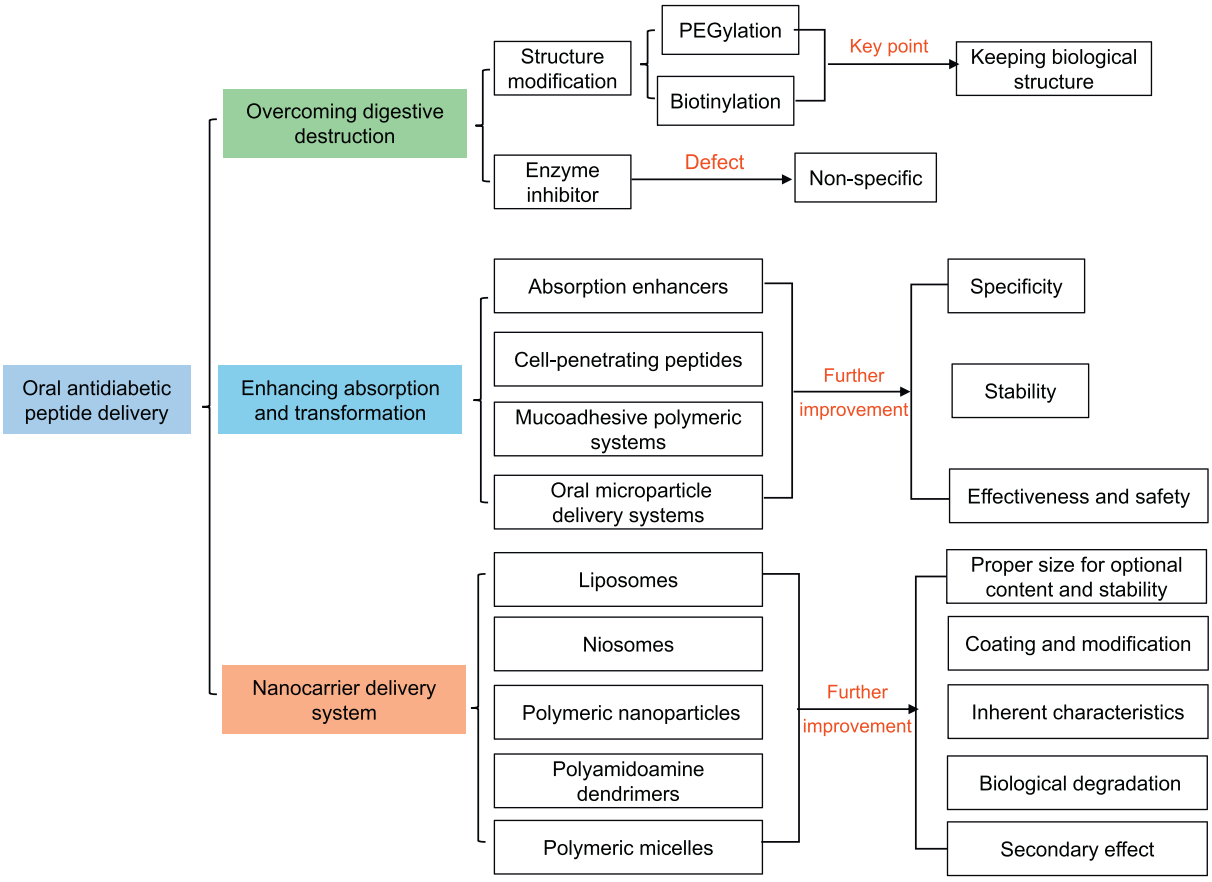

Fig. 2. Summary of different oral antidiabetic peptide delivery. Various methods for oral antidiabetic peptides have been developed to overcome the digestive destruction and the absorption barrier from the gastrointestinal tract. Structure modification of the peptides and enzyme inhibitors are useful way against the digestive destruction, meanwhile, the biological structure of peptides should be kept carefully, and the specificity of enzyme inhibitors also need improvement. As to the absorption barrier, enhancement of absorption and transformation via cell-penetrating peptides, mucoadhesive polymeric systems and oral microparticle delivery systems are all promising methods, while the specificity, stability, effectivity and safety should be evaluated carefully. Nanocarrier delivery system has shown tremendous effects on oral antidiabetic drug delivery. However, many factors including the particle size, coating, modification and the inherent characteristics of nanoparticles might affect the effectiveness of nanoparticles, the biological degradation of nano-materials and the secondary effect of nanoparticles should also be vigilant.

release of oral insulin, prolong its half-life and maintain the blood glucose level for up to 24 h in diabetic rats [97].

Biotin, also known as vitamin H or coenzyme R, is a water-soluble B vitamin that can be used to modify the surface of GLP-1. Biotin is helpful for enhancing the oral absorption ability of GLP-1 and protecting it against enzymatic degradation in the gastric and intestinal tracts. GLP-1 modified by biotin shows a higher absorption rate and better blood glucose control than native GLP-1 via the oral route in type 2 diabetic db/db mice [98].

Regardless of the type of modification of insulin, GLP-1 or its analogs for the oral route, the ultimate purpose of the modification is enhancement of the therapeutic function of the peptides. Their biological function should be retained carefully while the structures of peptides are modified to escape enzymatic degradation.

Another method to protect oral peptides from enzymatic degradation is to reduce the enzyme activity. Several enzyme inhibitors, for instance, soybean trypsin inhibitor, camostat mesylate, FK-448, and aprotinin, have been exploited to protect oral insulin from degradation caused by enzymes. After using a mucus-inert agent to enhance the mucus permeation of nanoparticles composed of insulin and trimethyl chitosan, oral insulin exhibited a higher bioavailability and a prominent hypoglycemic effect in diabetic rats [99].

Because these enzyme inhibitors are not specific, however, some undesired proteins or peptides are also absorbed, and the nutritive proteins involved in digestion can be disturbed; therefore, the safety of a long-term enzyme inhibitor for oral insulin or other peptide therapy remains controversial.

3.1.2. Enhancing the absorption and transformation of peptides

In addition to keeping the complete structure of peptides, transferring the peptides effectively through the mucus barrier, tight junctions, intestinal epithelial cells, and subepithelial tissue to the target organ, tissue or cell is pivotal for maintaining the function of peptides. According to previous studies, absorption enhancers, cell-penetrating peptides, mucoadhesive polymeric systems, microparticle delivery systems, and nanoparticle delivery systems have been used to promote the absorption and transfer of oral peptides.

3.1.2.1. Absorption enhancers. Absorption enhancers are substances that can change the properties of the intestinal epithelium, thus help peptides across the epithelia via either the paracellular or transcellular pathway. The underling mechanisms including weakening intestinal barriers integrity, breaking down tight junctions, decreasing mucus viscosity and/or increasing mucus fluidity. For example, chitosan and its derivatives can help to open the interepithelial tight junction and promote peptide transport [100]. In vivo experiments have shown that they display a tremendous impact on the absorption of oral insulin, resulting in hyperglycemic effect [100,101]. Thiomers are thiolated polymers that improve the permeation of macromolecular drugs through the gastrointestinal tract mucosa [102]. As penetration enhancers, they can also serve as potential vehicles for oral insulin delivery [103].

However, because these absorption enhancers lack specificity, they promote the penetration of not only peptide drugs but also intestinal toxins and pathogens that may induce local infection. In addition, they can damage the membrane of the gastrointestinal tract. Bile salts, nonionic surfactants, sodium dodecyl sulfate and lysolecithin can have intrinsic toxicity and can cause acute local damage to the intestinal wall and compromise cell viability [104]. Therefore, additional long-term studies are needed to certify the safety of absorption enhancers.

3.1.2.2. Cell-penetrating peptides. Cell-penetrating peptides are short peptides are primary composed of basic residues. They can interact with negatively charged cell-surface molecules through its positively charged amino acid residues (lysine, arginine), thereby help the peptides across the cell membrane. A recent study showed that cell-penetrating peptides enhanced the permeability and bioavailability of oral insulin in diabetes animal models [105]. In addition, insulin shows a greatly improved permeability through the intestinal mucus layer and epithelia after linking to cell-penetrating peptides and being encapsulated by mucoadhesive nanoparticles [105].

However, cell-penetrating peptides are not stable because they can be degraded by both extracellular and intracellular enzymes. More strategies, such as changing amino acid stereochemistry to improve the instability of cell-penetrating peptides, are necessary for their continued use in the future.

3.1.2.3. Mucoadhesive polymeric systems. As the first layer of the gastrointestinal tract, the intestinal mucosa significantly affects the absorption site, local diffusion and absorption rate of oral drugs. Mucoadhesive polymeric systems can maintain the tight contact between oral peptides and the mucosa as well as impede the metabolism of gastrointestinal enzymes, thereby increasing the oral bioavailability of peptides and proteins [106]. Furthermore, some mucoadhesive polymers can open the interepithelial tight junction and facilitate the transportation of peptide and protein. According to recent research, the combination of mucoadhesive polymers with oral insulin induces a significant increase in the circulating insulin level and reduces hyperglycemia [101,107]. Nevertheless, additional research is needed to clarify the effectiveness and safety of the clinical practice of mucoadhesive polymeric systems.

3.1.2.4. Oral microparticle delivery systems. Microencapsulation is the capsulation composed of microparticles between 1 and 1000 μm that can protect peptides from enzymes. When encapsulated in microparticles, drugs can be released at target sites via pH-dependent or other responsive mechanisms at a controlled rate [108]. By linking to microparticles, oral insulin can keep its complete structure and have a hypoglycemic activity comparable to subcutaneous injected insulin. In addition, microparticles can control the release rate of insulin and prolong its action time [109]. Because GLP-1 is rapidly cleaved at L-ala2 by DPP-IV, D-ala2-GLP-1 is resistant to DPP-IV but is lost within 4 h of injection. When encapsulated in the microspheres, oral D-ala2-GLP-1 can reduce glycaemia in diabetic mice for 8 h [110], whereas oral D-ala2-GLP-1 alone has no effect on glycemia.

Although the oral microparticle delivery system is helpful for oral insulin and GLP-1, the safety of oral microparticles in humans remains unclarified in the literature. Oral proteins and peptides undergo a complex procedure before they reach the target site. Every new attempt made by oral antidiabetic peptides has its own benefits and drawbacks, and many new technologies are limited to animal experiments. Therefore, more efforts are needed to find solutions for this complex problem. Apart from the above techniques, nanotechnology involves many new techniques, such as enzyme inhibition, cell-penetrating peptides, mucoadhesive polymeric systems and microencapsulation. The oral nanoparticle delivery system is likely a promising route for oral antidiabetic peptides, as described in detail below.

3.2. Nanocarrier delivery system

Nanotechnology is a science and technique in which single atoms or molecules are used to create materials ranging in size from 1 to 100 nm. Since the birth of nanotechnology in 1981, this technique has been used in various fields, such as microelectronics, computer technology, medicine, environmental science, energy, biotechnology and agriculture. Specifically, nanotechnology has been used widely in medicine delivery over the past few decades [111]. Filgueira et al. [112] used a novel nanochannel membrane device for drug delivery, and proved that the sustained, low-dose and constant release of the thyroid receptor-β-selective agonist GC-1 reversed high fat diet-induced obesity and normalized glycemia and serum cholesterol in mice. This nanochannel membrane device may be a candidate delivery device for antidiabetic drugs. The most important goal associated with hypoglycemic agents

is to achieve stable and satisfactory blood glucose control, which is closely related to the therapeutic route, absorption rate and bioavailability. Because the solubility and distribution of verified nanoparticles depend on their size, the absorption rate and bioavailability of medicines can be improved based on the size of the attached nanocarriers. Furthermore, antidiabetic peptides can be taken orally after being attached to nanocarriers [113]. Therefore, nano-based drug delivery systems play a pivotal role in hypoglycemic agent delivery.

Nanocarriers are traditionally categorized based on their constituents, namely, liposomes, niosomes, polymeric nanoparticles, polyamidoamines, and polymeric micelles, all of which have promising applications in novel diabetic therapies.

3.2.1. Liposomes

Phospholipid bilayers are important obstacles when medicines are transported into the cytoplasm or other organelles through a biological membrane. Therefore, liposoluble substances more easily cross the biological membrane. Liposomes are small vesicles consisting of phospholipid bilayers composed of natural non-toxic phospholipids and cholesterol via the phospholipid bilayers, the characteristics of which are similar to those of the biological membrane. Liposomes can fuse with the biological membrane and release their contents into the cytoplasm or other organelles, where this medicine can play its pharmacological role [114]. Liposomes modified with targeted ligand biotin can facilitate the transportation of insulin through the oral route [115]; however, the size of liposomes needed to achieve optimal content and stability requires additional research. Many other forms of liposomes exist, such as chitosan-coated, glycerolphosphate-chitosan, microcomplexation, sodium glycocholate and anionic liposomes used for oral peptides, insulin and GLP-1, which can promote absorption and protect these oral peptides from enzymatic or other forms of degradation [116–118].

3.2.2. Niosomes

Niosomes are composed of non-ionic surfactants incorporated with cholesterol as the excipient and can be categorized as unilamellar vesicles (100–3000 nm), small unilamellar vesicles (10–100 nm), or multilamellar vesicles based on their size and bilayers. Niosomes primarily act as drug reservoirs with sustained and prolonged drug release. Furthermore, they can change the solubility and biocompatibility of drugs. For diabetes therapy, niosomes have been used for insulin release via the vagina, and the prolonged insulin release from niosomes has achieved a better hypoglycemic effect than subcutaneous insulin injections in rats [119]. Furthermore, niosomes have been applied to other oral hypoglycemic agents, such as metformin and repaglinide, via the sustained release of niosomes; the bioavailability of oral hypoglycemic agents was enhanced, and the adverse effects and dosing frequency were significantly reduced [120].

3.2.3. Polymeric nanoparticles

Nanoparticles have been widely used in drug delivery systems in which adverse events are reduced and the drug utility is enhanced. Furthermore, researchers are trying to modify nanoparticles by attaching surface ligands to achieve new properties; specifically, this modification has been applied to antidiabetic drugs. For instance, the bioavailability of insulin loaded with nanoparticles via oral administration is low because it is poorly absorbed in the gastrointestinal tract, where the permeability is low. In diabetic rats, however, the pharmacological availability of orally delivered insulin loaded with nanoparticles attached to mucoadhesive agents significantly increases the bioavailability of insulin [105]. Insulin loaded with solid lipid nanoparticles can enhance the absorption of insulin and protect insulin from proteolytic degeneration in the gastrointestinal tract, thereby improving the bioavailability, blood residence time and tolerability of oral insulin in diabetic animals [121]. In addition, repaglinide-loaded solid lipid nanoparticles can increase the bioavailability of repaglinide due to their morphological features, loading parameters, particle sizes and drug release kinetics [122].

3.2.4. Polyamidoamine dendrimers

Dendrimers are synthetic nanosized macromolecules that are composed of branched subunits with a 3D structure. They have different compositions, such as polyamidoamine, polypropylenimine, liquid crystalline, core shell, peptide, glycol or hybrid forms, which yield different hydrophilicities, effective diameters and molecular weights. Dendrimers can be used as carriers of molecules such as genes, proteins or peptides [123]. When added to the dendrimer tool consisting of polyamidoamine, the secondary structure of insulin is maintained. In addition, polyamidoamine does not form a tight connection with proteins or influence protein conformation. Therefore, polyamidoamine dendrimers are a safe delivery tool for insulin, and their use can decrease insulin aggregation [124].

3.2.5. Polymeric micelles

Polymeric micelles are self-assembled amphiphilic *co*-polymers that form a core-shell micellar structure that can protect the drugs loaded on the core of micelles from enzymatic degradation. The branches of PEG can crosslink with each other in a PEG-PE micelle system and form a nanocage-like structure that can capture A and B chains of insulin. The two chains can recognize each other and form complete insulin again in the cage. Therefore, the micelle complex can protect oral insulin from aggregation and enzymatic degradation and promote the uptake of oral insulin via a transcellular and/or paracellular pathway, thereby ensuring the hypoglycemic function of oral insulin [125]. Micelles contain certain stimuli-responsive functional units that only react to specific signals, thereby forming a smart-cargo-release system. When co-loaded with this type of micelle, insulin can be released depending on the glucose level in the local microenvironment, thereby lowering the glucose level and avoiding hypoglycemia [126].

Nanocarriers have shown tremendous effects on oral antidiabetic drug delivery. They can protect oral peptides from degradation, target and smart release antidiabetic drugs, prolong their effect, lower the dosage, decrease toxic/side effects and enhance the therapeutic effect. However, many factors influence the effectiveness of nanoparticles, such as the particle size, coating, and modification as well as the inherent characteristics of nanoparticles [127]. Furthermore, clinicians should be vigilant with regard to the potential risks of nanoparticles, such as the biological degradation of nano-materials, the secondary effect of nanoparticles and other unknown biological effects [128,129]. Therefore, the application of nanotechnology in medicine, especially in diabetic therapy, has many opportunities and challenges.

3.3. Implantable drug delivery system

Apart from the aforementioned oral antidiabetic peptide delivery and nano-based drug delivery systems, an implantable drug delivery system is also an effective therapeutic route. The earliest and most commonly used implantable drug delivery system is that used for insulin delivery.

Because the main mechanisms of diabetes are insulin deficiency, insulin resistance, or both, insulin has been one of the key treatments for diabetes since the discovery of insulin in 1921. To make insulin therapy more effective, safe and convenient, researchers have tried various ways to make exogenous insulin purer, less irritative and closer to the physical mode. Alternative approaches for controlled insulin delivery have been extensively explored, including oral, nasal, pulmonary, transdermal and subcutaneous insulin delivery. The corresponding insulin formulations include oral insulin spray (Oral-lynt) [130], nasal sprays (Nasulin) [131] and inhaled insulin preparations (AERxs insulin) [132]. However, due to the poor permeability and the relevant high doses or low bioavailability of these insulin productions, the dream of "insulin tablets, capsules or sprays" remains challenging. From the

other hand, the technique of transdermal and subcutaneous insulin delivery has made encouraging progress [133,134]. The traditional mode of insulin delivery is via subcutaneous injection, and patient compliance is lowered by pain, mental stress and possible infection. Many attempts have been made to improve patient comfort level and compliance, such as insulin pump therapy and artificial pancreas and islet cell implantation, which can make diabetic therapy easier, safer, more stable and more comfortable.

3.3.1. Insulin pump therapy

The first insulin pump was developed in 1977. This externally worn device has a catheter embedded subcutaneously to deliver insulin [135]. This type of device remains in use in clinical practice, with a smaller pump, a battery with a longer life, a softer catheter and easier operation. Some pumps have remote control devices through which the insulin dose can be set based on a tested blood glucose level, where the recommended insulin dose is chosen by the connected computer. Compared with subcutaneous insulin injection, the insulin pump is more flexible, is advantageous in terms of the pharmacokinetics of insulin delivery, and can improve glycemic control with decreased insulin doses and fewer hypoglycemic events. However, it may be related to an increased frequency of diabetic ketoacidosis and local skin infection caused by catheter implantation [136].

The first implantable insulin pump was applied in 1979 [137]. This device was expected to simulate the function of the pancreas by delivering insulin via a catheter placed within the peritoneal cavity; however, the development of the implantable insulin pump was not smooth. Early implantable insulin pumps [135] were used via the intravenous or intraperitoneal pathway, with insulin in the pump and the tip of the catheter directed toward the liver. The insulin can be refilled transcutaneously via a refill port by dedicated doctors for at least 3 months, depending on the insulin requirements of each patient. The techniques associated with this equipment are complicated, and the insulin stored in the pump is less stable than that in a subcutaneous injection. In addition, it is associated with a high risk of thrombosis and infection. Therefore, several commercially produced pumps failed, and the application of this type of implantable insulin pump remains limited, despite its attractive technical characteristics [138]. In a limited number of patients, the safety, efficacy and tolerability of implantable insulin pumps were observed over prolonged use. The treatment satisfaction was higher than that with subcutaneous treatment, and the health-related quality of life of patients was high and stable during the research. However, no significant difference in the HbA1c level was observed, and more hyperglycemic time was observed with regard to continuous glucose monitoring sensor measurements [139]. Several studies have also reported the occurrence of anti-insulin antibodies following the implantation of insulin pumps in the 1990s, which may be related to a systemic immune reaction.

Besides, there are some studies toward osmotic pump system for other antidiabetic drugs. ITCA 650 is a miniature osmotic pump system that is designed to deliver zero-order, continuous subcutaneous release of exenatide at a precise predetermined rate for up to 12 months. Phase 3 clinical trial showed that compared with placebo, ITCA 650 significantly reduced HbA1c and body weight in uncontrolled T2DM patients with a baseline HbA1c 7.5% to 10% on oral antidiabetic medications [140]. Later study revealed that ITCA 650 also resulted in significant improvements in glycemic control in poorly controlled long-standing T2DM patients with a high baseline HbA1c >10% [141]. Moreover, patients with ITCA 650 therapy had significantly increased overall treatment satisfaction compared with those with twice-daily exenatide injections [142]. Thus, ITCA 650 could be a promising therapeutic approach for T2DM patients in the future.

3.3.2. Artificial pancreas

Can an insulin pump automatically control the release of insulin depending on the local glucose level, just like the natural pancreas? Based on this idea, physicians, scientists and engineers have worked together for over 50 years to develop complex automated closed-loop systems that can simulate the pancreatic regulation of glucose in healthy individuals. Consisting of an insulin pump, a continuous glucose monitoring sensor and a control algorithm, this closed-loop system can automatically detect the glucose level and change the insulin release accordingly, just like the human pancreas; therefore, it is known as the artificial pancreas [143]. Since the creation of the artificial pancreas, this closed-loop system has been considered as a bridge to the biological cure for diabetes, and different approaches have been attempted. Generally, two approaches to achieve blood glucose control for the artificial pancreas have been attempted: the unihormonal approach to control blood glucose level via insulin, and the bihormonal approach, which utilizes insulin, glucagon and pramlintide to improve glycemic control [144].

Recently, glucose-responsive insulin delivery systems have made admirable progress [134].Yu et al. [145] developed a novel glucose-responsive insulin delivery device using a painless microneedle-array patch in 2015. Microneedles of this “smart insulin patch” contain nanoparticles of glucose-responsive vesicles that consist of three components: insulin, glucose oxidase enzyme, and hypoxia-sensitive hyaluronic acid. As blood glucose levels rise, the enzymatic activity of glucose oxidase increases, creating a localized hypoxic environment which triggers the disassembly of the vesicles, releasing the insulin. The researchers had proven that it can not only regulate the high blood glucose to achieve normal levels, but also avoid the risk of hypoglycemia in mice models of type 1 diabetes. In 2018, Wang et al. [146] developed a painless core–shell microneedle array patch. This gel-based insulin delivery device can partially dissociate and subsequently release insulin when triggered by hydrogen peroxide (H_2O_2) generated during the oxidation of glucose by glucose oxidase enzyme inside the gel. Importantly, the bioresponsive core is coated with a protective shell which embeds H_2O_2-scavenging enzyme to protect normal tissues from injury caused by oxidative stress. Also, this insulin delivery device had been proven to effectively regulate the blood glucose levels within a normal range in diabetic mouse.

However, many challenges remain regarding the artificial pancreas. First, the main technical obstacle is the algorithm that helps patients to make real-time appropriate decisions according to their blood glucose levels [147]. Second, the accuracy and reliability of the data from the continuous glucose monitoring sensor may be the biggest obstacle, which is closely related to the risk of hypoglycemia [148]. Third, many biological or pathological states, such as exercise, concurrent illness, the effect of meals, and subcutaneous insulin kinetics in different diabetic patients, influence the accuracy of the algorithm and consequently affect the blood glucose control of the artificial pancreas [149]. Therefore, artificial pancreas system development is in great demand, especially with regard to the open-source control algorithms linking insulin delivery to real-time continuous glucose concentrations [150].

3.4. Islet cell transplantation

The major therapeutic goal of diabetes treatment is to achieve stable near-normal glycemic control without hypoglycemia, the avoidance of complications and a satisfactory life quality [151]. Although many antidiabetic medicines and delivery systems exist, achieving tight glycemic control is becoming increasingly difficult because of the progressive beta cell injury throughout the course of diabetes. Furthermore, hypoglycemic attacks secondary to tight glycemic control severely affect the quality of life of patients with diabetes. The artificial pancreas still has a long way to go to achieve smart glucose control. Therefore, imitating the physical function of the pancreas via islet cell transplantation may be the closest approach to representing the physical function of a healthy pancreas. In a five-year follow-up study, a significant consistent reduction of HbA1c without hypoglycemia was observed in all 10 patients with type 1 diabetes who had received transplants with single islet infusions [152]. Therefore, pancreatic islet transplantation has

become an attractive strategy for treating diabetes mellitus, especially for T1DM.

However, the long-term outcomes of islet transplantation are far from satisfactory [153]. Like the graft rejections associated with other transplantations, transplanted islet cells are eliminated immunologically due to early islet graft loss, which may be because of the HMGB1 protein secreted by damaged islet cells [154]. Islets must maintain their morphology and be revascularized quickly after transplantation to preserve glucose-stimulated insulin release. Besides, the perfect resource of islets is still unsolved. In addition, risks of bleeding, thrombosis, and elevation of portal pressure exist when islets are implanted via the portal vein into the liver. How to protect transplanted islets from elimination by the immune system has become the first problem associated with islet transplantation.

Biomaterials have been used to encapsulate long-term subcutaneous implants to overcome the foreign-body response of transplantation observed several decades ago [155,156]. Based on this idea, some biomaterials were used to build a permanent encapsulation device that could be implanted in a body to protect the foreign islets in this device from bodily elimination. This biocompatible implantable device consisted of a stainless-steel mesh with removable polytetra- fluoroethylene stoppers on each end that are implanted subcutaneously in the intracapsular region, and islets were implanted 40 days later using this device. The subcutaneous implantation of this device was well tolerated, and implanted islets showed a successful response to blood glucose [157]. Nevertheless, these materials are foreign objects that often generate an avascular fibrotic granular capsule and induce a chronic inflammatory response that can result in graft failure. Of note, recent advances in cell encapsulation technology including microencapsulation and macroencapsulation strategies make islet transplantation possible in the clinic [158,159]. Efforts on modifying the biomaterial chemistry of encapsulation, co-transplantation with cells capable of modulating immune responses have been made to avoid lifelong immunosuppression after islet transplantation [159].

To avoid the side effects of permanent foreign biomaterials, a new technique consisting of a subcutaneous device-less transplant that enables the successful transplantation of mouse or human islets was performed in mice. By placing an implantable device at the subcutaneous site, a prevascularized subcutaneous site composed of connective tissue and neovascularization is built via the controlled foreign-body response. Then, the implantable device is removed. Islets isolated and embedded in this artificial pocket can inhibit or terminate the foreign-body reaction [160]. This approach is effective in facilitating the implantation of insulin-producing cells, and different catheter materials with various surface properties and diameters have been tested for treatment optimization.

Due to the shortage of human pancreas donors, researchers have paid more attention on human embryonic stem cell (hESC)-derived islets and xenogeneic islets [161,162]. However, both of them have their own concerns. HESC-derived islets may conclude undifferentiated stem cells, while xenotransplantation tends to induce a potent immune response. The specific differentiation and purification for hESC are pivotal. Advanced imaging techniques along with β cell specific imaging probes may help the purification before islets transplantation and monitor the survival β cell mass after transplantation [163]. Although there are barriers to break down, the rapid progress in immune modulation approaches, cell encapsulation strategies, differentiation protocols of stem cells, device technology, and gene editing technology make islet transplantation a promising approach for the biological cure of diabetes [161,164].

4. Natural products

Although various drugs are used to treat T2DM, the development of novel antidiabetic drugs is currently emerging. Importantly, natural products (NPs, i.e., herbal medicines and their active ingredients) have been confirmed as possessing antidiabetic properties with less toxicity and fewer adverse effects [165–167]. The NPs that have been increasingly applied to treat T2DM primarily include flavonoids, terpenoids, polyphenols, alkaloids, saponins, and quinones [168]. These compounds widely exist in vegetables, herbs, fruits, and other plant-based foods. The potential mechanisms of NPs against T2DM occur through various targets and signaling pathways, including stimulating β-cells to release insulin, attenuating ER stress and oxidative stress-mediated damage in the pancreas to improve β-cell dysfunction, alleviating hepatic and skeletal muscle insulin resistance, modulating lipid accumulation and peroxidation, reducing inflammation, delaying the intestinal absorption of dietary fats, and, ultimately, reducing hyperinsulinemia and hyperglyceridemia [169,170]. Thus, NPs can regulate the expression levels of key proteins, such as PPAR-γ, PI3K-AKT, PKC, SREBPs, G6Pase, ERK, and JNK-FoxO1, and the NF-κB signaling pathways. In addition, some NPs effectively target specific proteins. For example, flavonoids stimulate GLUT4 translocation and inhibit the serum levels of DPP-4 to modulate glucose homeostasis in in vitro experiments [171,172]. Certain types of alkaloids achieve hypoglycemic and insulin-sensitizing capabilities by up-regulating GLP-1 secretion [173,174]. Moreover, anthocyanins enhance adiponectin and leptin secretion in adipocytes [175].

Of the various NPs, Berberine, an isoquinoline alkaloid extract isolated from the Chinese herb *Coptis Chinensis*, is widely known, and it has shown promising therapeutic action against diabetes and diabetes-related complications in animal and human studies. Many researchers have demonstrated that the administration of Berberine stimulates glycolysis by increasing glucokinase activity, increasing insulin section, and suppressing hepatic gluconeogenesis and adipogenesis by activating AMPK [176,177]. Berberine has also been shown to increase glucose-stimulated insulin secretion through elevated GLP-1 levels in Min6 β cells, attenuating reactive oxygen species production, reversing mitochondrial dysfunction and suppressing inflammation [178,179]. However, additional investigation should be performed because NPs are the leading promising compounds in the field of antidiabetic drug discovery.

5. Summary

Various types of antidiabetic drugs with different therapeutic targets have been tested, and the appropriate combination of these drugs is pivotal to achieve better glucose control and reduce diabetes-related complications. In addition to new drugs, therapeutics have kept pace with scientific innovation in novel treatment routes for patients with diabetes. Among these new routes, nanotechnology shows great potential as an antidiabetic drug delivery system with the advantages of greater efficiency, increased bioavailability, decreased toxicity and reduced dosing frequency. It is also widely applied in combination with other new therapeutic routes. Artificial pancreas and islet cell implantation are both promising methods for curing diabetes despite the obstacles that still need to be overcome. In addition, with the rapid progression of traditional Chinese medicine, NPs from herbs have become a promising therapeutic option for diabetes, although more research is needed to improve the technology and clarify the exact mechanisms underlying their clinical curative effects.

In light of the increasing burden of T2DM, any single medicine or method is far from sufficient in the battle against diabetes. In the future, novel treatment routes will be more widely used in glycemic control, and bring us new hope for the eradication of diabetes. Researchers will assess the effectiveness of the new approaches at multiple levels, including improving islet function, insulin resistance, complications, and prognosis. Although these new treatment routes are still immature, since the efficacy lacks long-term follow-up and evidence-based medicine data, and its mechanism also has many blind spots, we cannot deny its initial clinical effects and safety.

We believe that with the progress of clinical trials and basic research, there will be a large number of data to provide reliable support for the effectiveness, safety and prognosis of these new methods in the treatment of diabetes. It is extremely important to combine efforts from researchers across different disciplines to convert basic research into clinical medications.

Duality of interest

No potential conflicts of interest relevant to this article were reported.

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Author contributions

Cheng Hu and Weiping Jia conceived, designed, wrote and edited the manuscript. Weiping Jia is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data.

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