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Antidiabetic agents: Do they hit the right targets?

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Abstract

Diabetes mellitus (DM) is a progressive metabolic disease characterized by chronic hyperglycemia and caused by different degree of pancreatic islet dysfunction and/or insulin resistance (IR). Long course DM can lead to a variety of macrovascular and microvascular complications which involve artery vessels, heart, kidney, retina, nervous system, *etc*. In recent years, DM has attracted more and more attention due to its high morbidity and mortality. In addition to achieve effective glycemic control, prevention of complications has also been considered a priority for type 2 diabetes mellitus (T2DM) management. Herein, we provide a comprehensive overview on the pharmacotherapeutics for T2DM and perspectives on the future directions of basic and translational research on anti-diabetic therapy and pharmatheutical development of new drugs.

Keywords

diabetes mellitus; type 2 diabetes mellitus; anti-diabetic drugs; therapeutic target; glycemic control; insulin resistance; deficient insulin secretion; diabetic complications; polypharmacology.

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1 Introduction

Diabetes mellitus (DM) is a progressive non-communicable metabolic disease characterized by chronic hyperglycemia and pancreatic islet dysfunction, which eventually develops into a variety of severe macrovascular and microvascular complications, causing tremendous premature morbidity and mortality[1-3]. According to statistics by the International Diabetes Federation, diabetes caused 6.7 million deaths in 2021, and 537 million adults aged between 20 and 79 years old were living with diabetes; yet this number will likely rise up to 783 million by 2045. DM, particularly type 2 diabetes mellitus (T2DM), constitutes one of the most critical public health challenges of the twenty-first century, with enormous and continuous increasing economic and social burdens due to its high prevalence, severe co-morbidities, negative impact on quality of life, and life-threatening complications. Even worse is the prevalence of T2DM has reached approximately 10% of the global population and keeps rising rapidly worldwide. Asia has become the major region of emerging T2DM incidence with China and India being the top two epicenters[1-4]. As a metabolic disorder, the current global epidemic of T2DM is mainly driven by an unhealthy diet and a sedentary lifestyle, although genetic predisposition partly determines individual susceptibility to T2DM. At present, T2DM is primarily treated by the pharmacologic approach aiming to control blood glucose and minimize/postpone the associated complications. Anti-diabetic drugs are increasingly used worldwide, and the therapeutics has been continuously evolving with emerging new agents. Yet, the currently available anti-diabetic drugs do not present the desired efficacy but are generally associated with serious adverse effects. Herein, we intend to provide a comprehensive overview on the pharmacological therapy of T2DM and perspectives on the future directions of pharmacological research on anti-diabetic agents. Specifically, we summarize the published data with most updated information about our current understanding of the cell/molecular mechanisms for T2DM, the efficacy and mechanisms of various categories of anti-diabetic agents, the potential applications of some promising natural health products to the treatment of T2DM, and some of the novel anti-diabetic agents under development (undergoing clinical trials). We provide a balanced review and critical thoughts on the findings and discuss the current challenges and opportunities in pharmacological therapy of T2DM.

2 Basics of type 2 diabetes mellitus

Over 90% of DM cases belong to T2DM, and epidemiology of T2DM is affected by multiple non-modifiable and modifiable risk factors of complex combination of genetic, metabolic, and environmental factors that interact with one another[2-3,5]. The T2DM epidemic can be ascribed primarily to the global rise in obesity, sedentary lifestyles, high caloric diets, and population

aging[1]. T2DM is a multi-mechanism and multisystem disease, and therefore management of this pathological entity requires not only precise targeting of the diabetic mechanisms but also satisfactory avoidance of various complications especially cardiovascular complication. The prerequisite to achieve these goals is to have better understanding the mechanisms of T2DM (Fig. 1).

2.1 Deficient insulin secretion due to β-cell dysfunction

T2DM is a metabolic condition marked by deficient insulin secretion by pancreatic islet β-cells and tissue insulin resistance (IR)[2-3], which is manifested by loss of glucose homeostasis or hyperglycemia. In case of β-cell dysfunction, insulin secretion is reduced, which profoundly limits the body's capacity to maintain physiological glucose levels. β-cell dysfunction has been traditionally associated with β-cell death[6]. However, recent studies support that β-cell dysfunction in T2DM is consequent to a more complex network of interactions between the environment and various molecular pathways[7]. In obese population or subjects in an excessive nutritional state, hyperglycemia and hyperlipidemia are common characteristics that often cause IR and chronic inflammation. Such circumstances render β-cells under great toxic pressures created by lipotoxicity, glucotoxicity and glucolipotoxicity, which in turn result in inflammation, inflammatory stress, endoplasmic reticulum (ER) stress, metabolic/oxidative stress, and amyloid stress, ultimately leading to a loss of islet integrity thereby β-cell dysfunction with deficient insulin secretion [6-7].

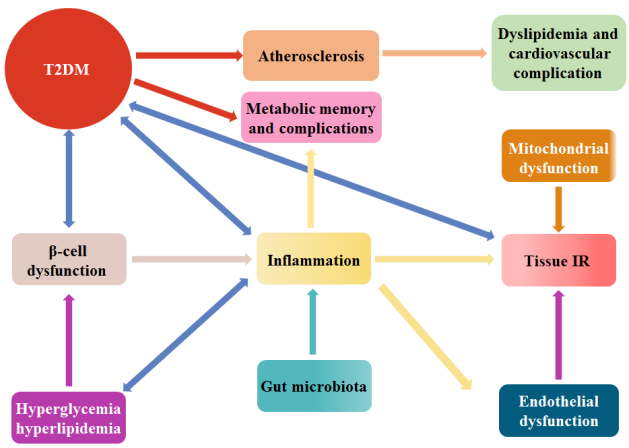

Fig. 1 T2DM is a multi-mechanism and multisystem disease, involving β-cell dysfunction, IR, dyslipidemia, inflammation, gut microbiota, mitochondrial dysfunction, cardiovascular complication and metabolic memory and diabetic complications

IR, insulin resistance; T2DM, type 2 diabetes mellitus.

2.2 Tissue IR

In regard with IR, however, insulin secretion may or may not be impacted, but glucose production in liver is increased whereas glucose uptake in muscle, liver, and adipose tissue is decreased. IR refers to a decrease in metabolic response of insulin-responsive cells to insulin or, at a systemic level, an impaired/lower response of cells/tissues/organs to circulating insulin[8-9]. In fasting state, insulin response is diminished by glucagon, glucocorticoids and catecholamines in order to prevent insulin-induced hypoglycemia. Catecholamines enhance lipolysis and glycogenolysis, whereas glucocorticoids promote muscle catabolism, gluconeogenesis and lipolysis. Hence, excessive secretion of these hormones is believed to account for the induction of IR[5,8-10]. Three main extra-pancreatic insulin-sensitive organs, skeletal muscle, adipose tissue, and liver, play major roles in the development of systemic IR, leading to T2DM.

In many cases, both β-cell dysfunction and IR processes take place together in the pathogenesis and development of T2DM, and the decrease of β-cell function gradually aggravates with the course of disease. Under such a circumstance, hyperglycemia is amplified leading to the progression of T2DM[11-12].

2.3 Dyslipidemia

Dyslipidemia is a common feature of T2DM, and increases the incidence of atherosclerosis and mortality of diabetic patients[13]. The hallmark of diabetic dyslipidemia is a characteristic dyslipidemia profile consisting of elevated triglyceride (TG), TG-rich lipoproteins, small dense low-density lipoproteins (LDLs), and reduced high-density lipoprotein (HDL) levels[14]. Although the pathophysiology of dyslipidemia in T2DM is still incompletely characterized, several factors such as hyperglycemia, IR, hyperinsulinemia, abnormalities in adipokines and adipocytokines have been implicated[15]. Epidemiological studies indicate that TG-rich lipoproteins contribute to atherogenesis and cardiovascular disease (CVD) risk[16-17].

2.4 Inflammation

Sustained high glucose levels increase proinsulin biosynthesis and islet amyloid polypeptides (IAAP) in β-cells, leading to the accumulation of misfolded insulin and IAAP and increase in the production of oxidative protein folding-mediated reactive oxygen species (ROS)[18]. These effects alter physiological ER Ca^{2+} mobilization and favor proapoptotic signals, proinsulin mRNA degradation and induce interleukin (IL)-1 β release that recruits macrophages and enhances local islet inflammation[7].

2.5 Gut microbiota

Gut microbiota is composed of many microbial species and recent evidence indicates that gut microbiota tremendously impact human physiology and participate in different biological processes[19]. A high-fat diet can induce up to threefold production of lipopolysaccharide (from Gram-negative bacteria) in mice models, thereby contributing to low-grade inflammation and IR[20]. Furthermore, intestinal dysbiosis can reduce short-chain fatty acid synthesis that promotes gut barrier integrity, pancreatic β-cell proliferation and insulin biosynthesis[21]. Dysbiosis can also compromise the production of other metabolites such as branched amino-acids and trimethylamine thus disrupting glucose homeostasis and triggering T2DM development.

2.6 Mitochondrial dysfunction

Evidence is emerging linking mitochondrial dysfunction to T2DM, age-related IR and associated complications[22-23]. Many damaging factors such as oxidative stress, defective mitochondrial biogenesis, genetic mutations, and aging can disrupt mitochondrial integrity causing mitochondrial dysfunction. Deregulated mitochondrial homeostasis with reduced mitochondrial biogenesis is a key component of mitochondrial dysfunction. The damage induced by excessive oxidative stress in mitochondria activates mitophagic processes in order to eliminate dysfunctional mitochondria or apoptotic cells[24]. The role of mitochondrial genetics is another risk of T2DM with several mitochondrial DNA (mtDNA) variants being associated with T2DM development[25-27].

2.7 Cardiovascular complication

T2DM is a multisystem disease with a strong correlation with CVD that is the major diabetic complication[28]. T2DM leads to a two- to four-fold increase in the mortality rate of adults from heart disease and stroke and is associated with both micro- and macro-vascular complications, with the latter accelerating atherosclerosis leading to severe peripheral vascular disease, premature coronary artery disease and increased risk of cerebrovascular diseases[28-30].

2.8 Metabolic memory and diabetic complications

Glycemic control is an important strategy in management of DM. However, the results of multiple large-scale clinical trials revealed that even with efficient glycemic control, diabetic complications persist, which is referred as "metabolic memory". This concept arose from the results of multiple large-scale clinical trials, which showed that even years before the diagnosis of diabetes, diabetes complications have already existed and progressed even when glycemic control is restored through pharmacological intervention[31-32]. Animal models of diabetes and *in vitro* cell cultures also subsequently confirmed that the initial hyperglycemic period results in permanent abnormalities (including aberrant gene expression) of target organs/cells[33-34]. It is now believed that metabolic memory involves four mechanisms: epigenetics[35-38], oxidative stress[39-40], non-enzymatic glycation of proteins and chronic inflammation.

In addition, low-grade inflammation, which is known to contribute importantly to T2DM and its vascular complications, has been shown to mediate metabolic memory. Many environmental factors (age, obesity, sedentarism and diet) that promote T2DM development trigger an inflammatory response leading to IR and endothelial dysfunction[41-42]. NF-κB activation in T2DM can induce the expression of inflammatory genes, which in turn enhances monocyte binding to endothelial and vascular smooth muscle cells, and subsequently promoting monocyte-to-macrophage differentiation[41]. In addition, NF-κB can also induces expression of inflammatory cytokines that are involved in vascular inflammation, with subsequent generation of endothelial adhesion molecules, proteases, and other mediators[42].

In theory, each of the T2DM-underlying mechanisms could be a therapeutic target for anti-diabetic drugs. In reality, however, as we can see from the following section, currently available anti-diabetic agents in clinical use mainly focus on a few of the multimechanisms for T2DM.

3 Contemporary anti-diabetic therapeutics

At present, hypoglycemic drugs that are commonly used in clinic are divided into nine categories, including biguanides, sulfonylureas, glitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl-peptidase IV (DPP-IV) inhibitors, sodium glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and insulin (Table 1). Most of the drugs are administered orally, except for a few of them, such as insulin and GLP-1RAs. There are other anti-diabetic drugs that are not commonly used in clinic, such as PPAR agonist, protein tyrosine phosphatase 1B (PTP1B) inhibitors, aldose reductase inhibitors (ARIs), α-glucosidase inhibitors and G protein-coupled receptor (GPCR) agonists (Table 2).

3.1 Biguanides

Biguanides are a class of hypoglycemic drugs of herbal origin, represented by metformin that has been widely used to treat diabetes since the 1950s[43]. Metformin is the first-line pharmacological choice for the management of hyperglycemia

Table 1 Contemporary anti-diabetic drugs

Hypoglycemic drugs	Advantages	Disadvantage	Function	Mechanism
Biguanides	The first-line pharmacological choice for T2DM	None	Suppressing hepatic gluconeogenesis and glucose output and promoting the uptake and utilization of glucose	Activating AMPK and inhibiting the transcription of gluconeogenic genes
Sulfonylureas	Specifically treating non-insulin-dependent DM	Hypoglycemia and weight gain	Stimulating insulin secretion and potentiating the biologic effect of the insulin	Binding to the SUR1
Glitinides (non-sulfonylureas)	Display excellent safety and efficacy and have low risk of hypoglycemia	The response to glinides varies Among individuals	Promoting the release of postprandial insulin	Inhibiting K_{ATP} in the pancreatic β-cell membrane and inhibiting KCNQ1
Thiazolidinediones	The only pharmacologic agents that specifically treat IR	Fluid retention, heart failure, weight gain, peripheral fractures, and macular edema	Increasing insulin sensitivity and inhibiting inflammation	Activating PPARγ
α-glucosidase inhibitors	Efficacy, safety, tolerability cardiovascular benefits, and lack of hypoglycemia	Not suitable candidates for other antidiabetic drugs and abdominal distension	Delaying intestinal carbohydrate absorption, Reducing postprandial glycaemia and saving insulin	Inhibiting upper gastrointestinal enzymes α-amylase and other α-glucosidases
Dipeptidyl-peptidase IV inhibitors	Have good security and are worthy of wide application if the indications are appropriate	Upper respiratory tract infection, nasopharyngitis, headache, urinary tract infection, arthralgia	Increasing insulin secretion and decreasing glucagon secretion	Enhancing GLP-1 preservation and expansion of β-cell mass through the inhibition of apoptotic pathways
Sodium glucose cotransporter 2 inhibitors	The combination of metformin and SGL T2 inhibitors	Urinary tract and genital infections, euglycemic diabetic ketoacidosis	Inhibiting the absorption of glucose from the proximal tubule of the kidney	Inhibiting the accumulation of M1-polarized macrophages and affecting inflammatory
Glucagon-like peptide 1 receptor agonists	The only islet G protein-coupled receptors in current clinical	Mild side effects of nausea, vomiting and hypersensitivity	Promoting insulin secretion of islet β-cells, inhibit appetite and delay gastric emptying	Activating GLP-1receptors

T2DM, type 2 diabetes mellitus; AMPK, adenosine monophosphate-activated protein kinase; K_{ATP}, ATP-sensitive potassium channel; PPARγ, peroxisome proliferator-activated receptor γ; GLP-1, glucagon-like peptide 1;PTPs, protein tyrosine phosphatases; IR, insulin resistance; SUR1, sulfonylurea receptors.

Table 2 New anti-diabetic drugs

Hypoglycemic drugs	Advantages	Disadvantage	Function
Insulin analogues	The most effective method of lowering blood glucose	Imitating natural insulin with exogenous one remains a challenge	Faster insulin absorption
PTP1B inhibitors	Favorable curing effects	The structural homologies of PTPs remains a challenge	Regulating insulin and leptin signal transduction negatively
ARIs	Applied to diabetic complications	Ineffective treatment of diabetes	Diminishing sorbitol flux through suppressing the polyol
G protein-coupled receptor agonists	Low risk of inducing hypoglycemia and gaining body weight	Failed to yield metabolic benefits in humans with T2DM	Enhancing insulin secretion and reduction appetite
Anti-diabetic phytochemicals	Prevention and management of T2DM with dietary polyphenols	Nadequate evidence	Inhibition of intestinal α-glucosidase and α-amylase, lens aldose reductase, *etc*
Resveratrol	Naturally occurring phytoalexin	Nadequate evidence	Reduction of blood glucose, improvement of insulin sensitivity, preservation of pancreatic β-cells, alleviation of diabetic complications
Curcumin	A bioactive constituent	Unknow	Improving the function and prevention death of β-cells, and decreasing IR
Berberine	An adjuvant treatment of T2DM, hyperlipidemia, and hypertension	Unknow	Increasing insulin receptor expression

ARIs, aldose reductase inhibitors; T2DM, type 2 diabetes mellitus; PTP1B, protein tyrosine phosphatase 1B; IR, insulin resistance; PTPs, protein tyrosine phosphatases.

in T2DM and improves glycemic control without inducing hypoglycemia or weight gain[44]. The efficacy of metformin has been confirmed by many experiments, one of which is a randomized clinical trial of intensive *vs.* standard glycemic control among patients with newly diagnosed T2DM[45-46]. Metformin is believed to act by suppressing hepatic gluconeogenesis and glucose output on one hand and promoting the uptake and utilization of glucose in skeletal muscles and adipose tissues to normalize blood glucose level on the other hand, based on numerous animal and human studies[47]. Also important is that metformin has certain insulin-sensitizing effects likely by acting in the gut lumen through multiple mechanisms. Among high risk patients with prediabetes and IR, metformin reduces the risk of developing diabetes[48].

In addition to its hypoglycemic and insulin-sensitizing effects, metformin also has protective effects on cardiovascular system[45] and beneficial actions on Alzheimer's disease through improving cognitive impairment and memory loss[49]. A clinical trial found lower rates of myocardial infarction and mortality in a subgroup of overweight patients randomly assigned to metformin compared with conventional (diet) therapy[45]. Moreover, metformin can

also exert many other favorable effects beyond its glucose-lowering action, among which are anti-inflammatory, anti-cancer, immunomodulatory effects, as well as reduction of free fatty acids and improvement of endothelial dysfunction[50-53]. Evidence also exists indicating that metformin prolongs lifespan by activating autophagy and adenosine monophosphate-activated protein kinase (AMPK) which inhibits mTOR[54]. It should be noted that interest in metformin for other uses remains yet to be supported by solid clinical evidence[47].

While it appears that metformin has a hundred merits and not a single demerit due to its pleiotropic property, a full understanding of the mechanisms of action remains elusive. Nonetheless, this drug is known to produce its effects primarily by activating AMPK, increasing the absorption of intestinal glucose and the level of GLP-1, and improving gut microbiome[55]. At the molecular level, metformin improves insulin sensitivity by inhibiting the transcription of gluconeogenic genes thereby the expression of the corresponding protein products and lipogenesis[56].

Because of its multiple effects, metformin has been widely used either alone or in combination with other agents in T2DM patients. Overall, six decades of clinical uses indicate no major safety concerns for metformin, except for subclinical increases in lactic acid or lactic acidosis in extreme overdose or improper selection of indications [46].

It is known that patients with T2DM is associated with both poorer clinical outcomes during the corona virus disease 2019 (COVID-19) pandemic and an increased risk of death in hospitalized COVID-19 patients. Thus, it is natural and rational to speculate the potential benefit of anti-diabetic agents in improving the prognosis of COVID-19 patients. Indeed, the role of glucose control has been emphasized for such a purpose[57-59]. it may be speculated that this biguanide might positively influence the prognosis of patients with T2DM hospitalized for COVID-19. The available data from observational retrospective studies present strong evidence for significant reduction in mortality in metformin users compared with non-users. A meta-analysis on four retrospective analyses of observational studies in patients with T2DM hospitalized for severe COVID-19 suggests a positive effect (whether statistically significant or not) in all four studies with an overall reduction of death by 25%[60-61]. For example, a large US study of 6 256 COVID-19 patients with T2DM (52.8% female, mean age 75 years) associated metformin with significant reduction of mortality in women, but not in men[62]. These studies indicate the potential novel application of metformin to COVID-19 patients with T2DM for rescuing the lives and meanwhile achieving effective control of glucose on one hand and support the importance of glycemic control to related conditions other than diabetes on the other hand. Nonetheless, given the inherent confounding nature of observational studies, caution must be taken before drawing any firm conclusions in the absence of randomized controlled trials.

3.2 Sulfonylureas

Sulfonylureas are commonly used as insulin secretagogues. Sulfonylurea drugs are usually categorized as being first-, second-generation and vary in terms of their dosages and effectiveness in treating T2DM[63]. The first-generation sulfonylureas mainly include tolbutamide, chlorpropamide, acetohexamide and tolazamide, and the second-generation sulfonylureas such as glyburide, glipizide and glibornuride have a more nonpolar or lipophilic side chain, which results in a marked increase in their hypoglycemic potency. Although controversies exist as to the usefulness of sulfonylureas, evidence is generally in favor of their use in T2DM with poor islet function[64]. When used properly, the sulfonylurea drugs lower plasma glucose concentrations in diabetic patients by stimulating insulin secretion and by potentiating the biologic effect of the insulin on tissues as skeletal muscle, fat, and liver. Moreover, sulfonylureas can reduce the clearance rate of insulin in liver, resulting in increased insulin levels[65], and prevent α cells from secreting glucagon[66]. Furthermore, sulfonylureas can also improve the sensitivity of peripheral tissues to insulin by binding and activating peroxisome proliferator-activated receptor γ (PPARγ) receptor[67] and promote the utilization of peripheral glucose[68]. In addition to their hypoglycemic effect, these drugs can also inhibit the proliferation of vascular smooth muscle cells and prevent the progression of DM-related atherosclerosis[69-71]. The main adverse effect of sulfonylureas is long-lasting hypoglycemia, which may lead to permanent neurological damage and even death in elderly subjects who are exposed to some intercurrent events, *e.g.*, acute energy deprivation or a drug interaction. The first generation of sulfonylureas has severe cardiovascular safety issues, and the second and third generation sulfonylureas do not increase the risk of all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke[72]. However, at present, there is no consensus on cardiovascular safety of sulfonylureas. There is also a hypothesis that sulfonylureas may be related to hypertension by hindering the relaxation of vascular smooth muscle, but it needs to be further confirmed[73]. Although sulfonylureas have side effects such as hypoglycemia and weight gain, they could be used carefully according to patient's conditions.

Regarding the mechanism of action, sulfonylureas act mainly by binding to the sulfonylurea receptors (SUR1) of

ATP-sensitive potassium channel (K_{ATP}) in β-cells to inhibit potassium efflux and depolarize cell membrane so as to stimulate insulin secretion in a glucose-independent manner[74]. Some of the first generation sulfonylureas can also interact with the sulfonylurea receptors in cardiomyocytes (SUR2A) and vascular smooth muscle (SUR2B) cells, resulting in the disturbance of cardiac conduction in myocardial infarction[75]. Through a similar mechanism, sulfonylureas stimulate the secretion of somatostatin and suppress the secretion of glucagon in δ-cells and α-cells[76-77]. Sulfonylureas seem to exert other effects as well: they increase peripheral glucose utilization by two mechanisms of action, stimulating hepatic gluconeogenesis, and increasing the number and sensitivity of insulin receptors[78]. Impairment of the effect on insulin secretion that occurs during chronic administration of sulfonylureas is due to the downregulation of the receptor of sulfonylureas on the surface of β-cells.

3.3 Glitinides (non-sulfonylureas)

Compared with sulfonylureas, glinides, including repaglinide, nateglinide, and mitiglinide, are rapid-acting insulin secretagogue that mimics early-phase insulin release, thereby providing better control of the postprandial glucose levels. For instance, repaglinide, which is known as an oral non-sulfonylurea insulin secretagogue, plays a powerful role in postprandial blood glucose reduction by promoting the release of postprandial insulin. It is widely used in patients with renal insufficiency for the reason that it is mainly metabolized in the liver by the cytochrome P450 (CYP) 3A4 enzyme system with a low risk of hypoglycemia[79]. Of note, studies have shown that repaglinide can be used in early treatment of cystic-fibrosis-related diabetes[80]. Compared with repaglinide, nateglinide, another glinide drug, has a faster onset and shorter action time. Additionally, it has been reported that glinides have long-term protective effects on β cell function and cardiovascular tissue[79]. Moreover, glinides have been widely used clinically and display excellent safety and efficacy and are associated with lower risk of hypoglycemia in comparison to sulfonylureas. Therefore, glinides are a good choice for monotherapy or combination therapy. However, the response to glinides varies among individuals, which is partially due to genetic factors involved in drug absorption, distribution, metabolism, targeting and different stages of disease.

Mechanistically, glinides stimulate insulin secretion by inhibiting K_{ATP} in the pancreatic β-cell membrane. In addition to binding to SUR like sulfonylureas, repaglinide also binds to a unique site and blocks K_{ATP} in β-cells[81], which depolarizes the cell membrane to enhance calcium influx, eventually resulting in the release of insulin[82]. Repaglinide improves insulin sensitivity, and this effect is strengthened by inhibiting KCNQ1, the α-subunit of slow delayed rectifying potassium channel[83-84].

3.4 Thiazolidinediones

It is known that hyperglycemia occurs only when insulin secretion is insufficient to overcome barriers to insulin action. Thus, when insulin action is normal, hyperglycemia occurs when absolute insulin secretion is deficient. In contrast, when insulin action is impaired (IR), hyperglycemia occurs when insulin secretion is inadequate to overcome IR. IR increases the prevalence of T2DM sixfold[85]. Thiazolidinediones, mainly including pioglitazone and rosiglitazone, are the pharmacologic agents that specifically treat IR. These drugs act as PPARγ agonists to increase insulin sensitivity and inhibit inflammation. Besides, thiazolidinedione can reduce fat deposition in liver, muscle, and pancreas, thus protecting them from the deleterious effects of free fatty acids. Importantly, thiazolidinedione provides long-term protection owing to the fact that progression of diabetes is delayed even if the drug is discontinued[86]. Astonishingly, studies have shown that rosiglitazone can continuously reduce fasting blood glucose for 3.5 years[87].

The metabolic consequences of IR are increased risk of T2DM and associated cardiovascular diseases[85]. In this regard, the beneficial effects of thiazolidinediones on cardiovascular risk factors associated with IR have been well documented. In addition, thiazolidinediones also have protective effects on vascular endothelium[88]. Thiazolidinediones can reduce blood viscosity and platelet aggregation induced by IR. Furthermore, thiazolidinediones can reduce blood pressure, improve heart function, and promote fibrinolysis[89]. In addition, thiazolidinediones can also protect the kidney through a variety of mechanisms, including repressing inflammation and oxidative stress, reducing lipid deposition, improving renal microcirculation, and inhibiting the proliferation of glomerular and tubular cells, thus ultimately reducing the excretion of urinary protein, as well as preventing glomerulosclerosis and tubulointerstitial fibrosis[90-95]. Thiazolidinediones are now generic and less costly than pharmaceutical company-promoted therapies and are the most effective pharmacologic agents for treating IR.

However, the use of thiazolidinediones has been limited because of the concern about the safety issues and side effects: there were increasing concerns about the thiazolidinediones-induced increases in fluid retention, risk of heart failure, weight gain, and peripheral fractures, and adverse effects on macular edema[96]. Thus, the use of these previously extensively prescribed and effective treatments for T2DM has been remarkably diminished because of concerns. To a certain extent, the above-mentioned renal protective effects of thiazolidinediones could also be

ascribed to the inhibition of RAAS system[97].

3.5 Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs), including acarbose, miglitol, and voglibose, are recommended for therapy by the international Diabetes Federation (IDF)[98] and American Association of Clinical Endocrinologists (AACE)[99]. Their efficacy, safety, tolerability, cardiovascular benefits, and lack of hypoglycemia make them suitable for T2DM. They may also be used in patients with impaired glucose tolerance and can delay the occurrence of T2DM in these patients. They are particularly useful for patients who are at risk of hypoglycemia or lactic acidosis, and thus, are not suitable for other antidiabetic drugs such as sulfonylureas and metformin.

Acarbose is a commonly used AGIs in clinic and it works by inhibiting upper gastrointestinal enzymes α-amylase and other α-glucosidases that break down complex carbohydrates into glucose, thus preventing absorption of starch and other carbohydrates from the brush border of the intestine and reducing postprandial glucose to improve glycemic control[100-101]. It also has an insulin-sparing effect and can increase incretin hormones and glucagon like peptide-1 but inhibit the postprandial release of gastric inhibitory polypeptide (GIP), helping reduce body weight[102]. Although acarbose may sometimes cause abdominal distension, it can effectively reduce weight and postprandial blood glucose, thus delaying the progression of prediabetes due to impaired glucose tolerance (IGT) to T2DM and reducing the risk of hypertension and CVD in IGT patients[103]. Moreover, acarbose can ameliorate vascular endothelial dysfunction and promote angiogenesis and wound healing, which may probably be mediated by the Akt/eNOS signaling pathway[104]. In addition, acarbose has been shown to prolong lifespan and enhance survival rate *via* decreasing postprandial blood glucose and insulin levels[105]. It is also reported that the intestinal microbiota play a significant role in life extension of acarbose[106]. Low-grade albuminuria, namely urinary albumin to creatinine ratio (UACR) < 30 mg/g, was reported to be associated with many cardiovascular risk factors and diabetic nephropathy[107-108]. Both acarbose and metformin can ameliorate low-grade albuminuria of T2DM[109].

Overall, this class of compounds delays intestinal carbohydrate absorption, reduces postprandial glycaemia, and helps manage diabetes. Voglibose and miglitol inhibit the disaccharide-digesting enzymes but have no effect on the starch digesting enzyme α-amylase[110-111]. Of note, miglitol alleviates myocardial ischemia *via* inhibiting the decomposition of glycogen in myocardium, affecting ATP sensitive potassium channel, and activating GLP-1[112]. Miglitol may inhibit myocardial apoptosis by reducing the expression of Bax protein and the production of hydroxyl radical[113]. In addition, miglitol has inhibitory effect on α-glucosidase of human intestinal microflora[114]. AGIs can also exert beneficial effects on lipid metabolism and the treatment of acquired immune deficiency syndrome (AIDS) and tumors[115-117]. Collectively, AGIs are an effective, safe, and well tolerated treatment for diabetes, which provide cardiovascular benefits as well and can be used as monotherapy, combination therapy with other oral drugs and insulin, or fixed-dose combinations[118].

3.6 Dipeptidyl-peptidase IV inhibitors

DPP-IV inhibitors are ubiquitous enzymes that act on incretin hormones, mainly GLP-1 and gastric inhibitory peptide (GIP), which are critical for maintaining glucose homeostasis through increasing insulin secretion and decreasing glucagon secretion. By inhibiting the DPP-IV enzyme, DPP-IV inhibitors (alogliptin, sitagliptin, saxagliptin, linagliptin), also known as gliptins, increase the levels of GLP-1 and GIP, which in turn increase β-cell insulin secretion in pancreas, thereby reducing postprandial and fasting hyperglycemia[119]. On the other hand, glycemic variability is an emerging target for preventing complications related to T2DM, and DPP-IV inhibitors have shown their superior effectiveness in reducing glycemic variability compared to other oral anti-hyperglycemic drugs (OADs)[120]. A systematic review and meta-analysis of randomized controlled trials (RCTs) were performed to evaluate the effect of DPP-IV inhibitors compared with other anti-hyperglycemic drugs on glycemic variability[121].

The findings indicate that DPP-IV inhibitors are promising alternatives for reducing glycemic variability in T2DM patients. Pharmacologically, DPP-IV inhibitors enhance GLP-1 preservation and expansion of β-cell mass through the inhibition of apoptotic pathways and improve blood glucose control without inducing hypoglycemia[122-123].

In addition, vildagliptin has anti-inflammatory and lipid-improving effects[124]. Vildagliptin can protect against vascular diseases[125]. Furthermore, studies have shown that sitagliptin yields protective effects on the heart of mice and improves myocardial ischemia[126-127]. DPP-IV inhibitors can improve IR and inhibit liver inflammation and steatosis, therefore probably being used in the treatment of nonalcoholic fatty liver disease (NAFLD) in the future[128]. Sitagliptin was reported to have beneficial effects on intestinal flora[129]. DPP-IV inhibitors can protect vascular endothelium and prevent atherosclerosis, and the actions are independent of GLP-1 and GIP[130]. DPP-IV inhibitors might probably be used for the treatment of inflammatory bowel diseases (IBD) in the future [131]. Notably, DPP-IV inhibitors improve cardiac remodeling mainly through the following mechanisms: anti-inflammation, anti-

oxidative stress and anti-cardiac fibrosis, thus exerting a preventive role in atrial fibrillation[132].

Overall, DPP-IV inhibitors have good safety profiles and are worthy of wide application if the indications are appropriate. Although saxagliptin was associated with an increased rate of hospitalization for heart failure, DPP-IV inhibitors do not in general increase risk of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke when compared to placebo in T2DM patients[133-134]. However, DPP-IV inhibitors can elicit some adverse effects. The most common side effects noticed in DPP-4 inhibitors sitagliptin and saxagliptin are upper respiratory tract infection, nasopharyngitis, headache, urinary tract infection, and arthralgia. They can also induce arthritis and arthralgia through various mechanisms such as cytokines release and inflammatory response[135]. It has been reported that DPP-IV may be negatively correlated with cancer, hence, long-term inhibition of DPP-IV enzyme in cancer may be detrimental[136]. However, some studies have also shown that DPP-IV inhibitors have anticancer properties due to cytotoxic effects[137].

3.7 Sodium glucose cotransporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the latest class of antidiabetic medications that work by inhibiting the absorption of glucose from the proximal tubule of the kidney and hence cause glycosuria, exerting a strong effect in reducing blood glucose. Four SGLT2 inhibitors are currently in clinical use, including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. SGLT2 inhibitors reduce glycated hemoglobin by 0.5%-1.0%, improve glycemic control (fasting and postprandial), and reduce body weight[138]. Due to the virtue of no interference with insulin action and secretion, their efficacy remains the same even in presence of progressive β-cell dysfunction in T2DM. A meta-analysis unraveled that SGLT2 inhibitors achieved better glycemic control and greater weight reduction than DPP-IV inhibitors without increasing the risk of hypoglycemia in patients with T2DM that is inadequately controlled with insulin[139]. Recent clinical guidelines have suggested the use of SGLT2 inhibitors as add-on therapy in patients for whom metformin alone does not achieve glycemic goals, or as initial dual therapy with metformin in patients who present with higher glycated hemoglobin (HbA1c) levels[140]. Moreover, the addition of other beneficial actions on the top of improved glycemic control with a low risk of hypoglycemia with the combination of metformin and SGLT2 inhibitors is another attraction. However, caution needs to be taken of increased risk of euglycemic diabetic ketoacidosis during combination therapy.

In addition to their hypoglycemic action, SGLT2 inhibitors can also produce protective effects on a variety of organs/systems. One of these beneficial actions is to reduce cardiovascular events, particularly heart failure, in cardiovascular outcome trials[141]. First, SGLT2 inhibitors have demonstrated impressive cardioprotective and reno-protective effects, and favorable effectiveness in reducing body weight, blood pressure, lipid profile, arterial stiffness, and endothelial function. Excessive sympathetic activity can result in increased arterial stiffness, endothelial dysfunction, and fluid retention[142-144]. SGLT2 inhibitors can alleviate sympathetic overactivity and reduce preload and afterload, thus lowering blood pressure without reflexive heart rate acceleration[145]. Studies have shown that empagliflozin improves endothelial function and delays the progression of aortic atherosclerotic plaque[146]. Of note, SGLT2 inhibitors can reduce the risk of heart failure and cardiac hypertrophy[147]. SGLT2 inhibitors may achieve cardiovascular protection through a variety of mechanisms, such as lowering blood pressure, correcting electrolyte disorders, alleviating mitochondrial dysfunction, improving energy metabolism, and suppressing cardiac fibrosis[148-149]. Second, SGLT2 inhibitors play a protective role in kidney by reducing urinary protein, constricting renal afferent arterioles, promoting uric acid excretion, inhibiting renal inflammation, attenuating the expression of fibrosis genes, and increasing autophagy, eventually postponing renal failure[150-154]. Besides, SGLT2 inhibitors can prevent podocyte loss, reduce renal lipid accumulation, thus delaying the progression of nephropathy[155]. SGLT2 inhibitors can reduce liver fat deposition and improve liver function with or without weight loss, thus yielding a certain therapeutic effect on NAFLD[156-158]. Chronic low-grade inflammation is a key factor for the development of T2DM and associated complications, especially atherosclerosis and coronary artery disease[159-161]. SGLT2 inhibitors can improve the function of adipose tissue through inhibiting the accumulation of M1-polarized macrophages and mitigating the levels of proinflammatory factors, such as adiponectin and leptin which can promote cardiac and renal fibrosis, thereby improving IR, attenuating inflammation and improving vascular endothelial function[162-165]. Additionally, dapagliflozin has been documented to reduce the activation of inflammatory bodies and regulate the phenotypic polarization of macrophages, thus resulting in ameliorating myocardial fibrosis[166-167]. Moreover, SGLT2 inhibitors can also attenuate inflammatory response of skeletal muscle and nervous system[168]. Furthermore, SGLT2 inhibitors are reported to have anti-cancer properties, for example, ipragliflozin suppresses the proliferation of breast cancer cells[169]. Nonetheless, SGLT2 inhibitors may increase the risk of stroke[170].

The main adverse events of SGLT2 inhibitors include urinary tract and genital infections, as well as euglycemic diabetic ketoacidosis. Concerns have also been raised about the association of SGLT2 inhibitors with lower limb amputations, Fournier gangrene, risk of bone fractures, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury[171]. SGLT2

inhibitors can occasionally cause skin reactions, such as systemic rashes and urticaria[172].

3.8 Glucagon-like peptide 1 receptor agonists

GLP-1 is an endogenous incretin released from gut enteroendocrine cells, which yields many beneficial effects through binding to its receptor. GLP-1 can inhibit appetite, delay gastric emptying, inhibit the secretion of glucagon by islet α-cells, improve vascular endothelial function, lower blood pressure, and most importantly promote insulin secretion of islet β-cells[173-174]. These advantages make GLP-1 receptor an excellent target for T2DM management. GLP-1RAs are a class of drugs with a well-established efficacy and safety profile in patients with T2DM. Compounds belonging to GLP-1RAs are primarily derived from modifications based on either exendin-4 (a compound present in Gila monster venom) or human GLP-1 active fragment[175]. GLP-1RAs can be divided into two categories according to their differences in pharmacodynamics: short-term acting exenatide and lixisenatide and long-term acting albiglutide, dulaglutide, exenatide, liraglutide, and semaglutide. Short-term acting GLP-1RAs primarily delay gastric emptying (lowering postprandial glucose) and long-term acting agents affect both fasting glucose (*via* enhanced glucose-dependent insulin secretion and reduced glucagon secretion in the fasting state) and postprandial glucose (*via* enhanced postprandial insulin secretion and inhibition of glucagon secretion)[176]. Aside from their main mechanism of action, GLP-1RAs can also activate autophagy, *e.g.*, exendin-4 reduces β-cell damage by improving autophagy clearance[177-179].

In addition to their hypoglycemic efficacy, GLP-1RAs can reduce cardiac reperfusion injury, which may be helpful to the treatment of myocardial infarction[180]. In addition, exendin-4 improves cardiac remodeling and diastolic dysfunction[181], and liraglutide reduces the accumulation of fibroblasts and collagen deposition, thus improving cardiac fibrosis[182]. GLP-1RAs also produce neuroprotective and neurotrophic effects to improve the symptoms of Alzheimer's disease and Parkinson's disease[183-185]. Exendin-4, a GLP-1 analogue, can inhibit renal inflammation, reduce proteinuria, improve renal function and alleviate renal fibrosis[186]. Moreover, GLP-1RAs have a beneficial effect on blood lipids, which is manifested by the decrease of chylomicrons and triglycerides[187-188]. GLP-1RAs lessen hepatic fatty degeneration, inflammation, and hepatic fibrosis[189], as well as lung inflammation and fibrosis[190].

GLP-1RAs have mild side effects of nausea, vomiting and hypersensitivity. Some studies have shown that GLP-1RAs are related to the occurrence of gallbladder diseases, such as gallstones and acute cholecystitis[191-193].

4 New anti-diabetic drugs under development

4.1 Insulin analogues

Insulin remains a predominant life-saving medication for both T1DM and T2DM because insulin therapy is the most effective method of lowering blood glucose. Endogenous insulin secretion can restrict the fluctuation of the high surge of blood glucose levels, while imitating natural insulin with exogenous analogues remains a challenge as different insulin analogs (rapid acting, short acting, intermediate acting, and long acting) have different pharmacokinetic and pharmacodynamic properties and inconsistent effectiveness in overall hyperglycemia level and nocturnal hypoglycemia. Thus, whether the use of insulin analogues is appropriate is still a question in great scientific debate.

A systemic review included 10 trials involving a total of 2 751 participants with 1 388 being randomized to receive insulin analogues and 1 363 to receive regular human insulin[194]. The duration of intervention ranged from 24 to 104 weeks, with a mean of about 41 weeks. The trial populations showed diversity in disease duration and inclusion and exclusion criteria. The analysis found no clear benefits of short-acting insulin analogues over regular human insulin in people with T2DM. Overall, the results from the 10 RCTs failed to provide solid evidence in favor of use of insulin analogues with insufficient data on patient-relevant outcomes, like all-cause mortality, microvascular or macrovascular complications and severe hypoglycemic episodes.

Another meta-analysis compares the effects of long-term treatment with ultra-long-acting insulin analogues (insulin glargine U100 and U300, insulin detemir and insulin degludec) with NPH (neutral protamine Hagedorn) insulin (human isophane insulin) in adults with T2DM[195]. This analysis included 24 RCTs, of which 16 trials compared insulin glargine to NPH insulin, and eight trials compared insulin detemir to NPH insulin. In these trials, 3 419 patients with T2DM were randomized to insulin glargine and 1 321 to insulin detemir. The duration of the included trials ranged from 24 weeks to five years. The results show that while the effects on HbA1c were comparable, treatment with insulin glargine and insulin detemir resulted in fewer participants experiencing hypoglycemia when compared with NPH insulin. Treatment with insulin detemir also reduced the incidence of serious hypoglycemia. Approximately 1% patients treated with insulin detemir instead of NPH insulin benefited. It should be noted that in these trials, low blood glucose and HbA1c targets were set, which correspond to near normal or even non-diabetic blood glucose levels. Therefore, the authors concluded that the results from the trials are only applicable to people in whom

such low blood glucose concentrations are targeted, which does not conform to the current guidelines recommending less-intensive blood glucose lowering for most patients with T2DM in daily practice (*e.g.*, people with cardiovascular diseases, a long history of T2DM, who are susceptible to hypoglycemia or older people). Additionally, the low-certainty evidence and trial designs that did not meet the current clinical practice guidelines render it unclear whether consistent effects could be achieved in daily clinical practice.

Although the clinical efficacy of regular human insulin has been well appreciated over 35 years, rapid-acting insulin analogues (insulin lispro, insulin aspart, and insulin glulisine) offer a couple of clinical advantages over regular human insulin. First, rapid-acting insulin analogues are engineered with a reduced tendency to aggregate as hexamers, which allows for rapid dissociation and absorption after a subcutaneous injection. Second, the more recently developed fast-acting insulin aspart (faster aspart) is an ultrafast-acting mealtime insulin that contains the conventional insulin aspart in a new formulation with the excipients niacinamide and L-arginine to achieve faster insulin absorption than regular human insulin and the conventional insulin aspart formulation[196].

4.2 PTP1B inhibitors

PTP1B is the main enzyme involved in insulin receptor desensitization by acting as a negative regulator of insulin and leptin signal transduction and is considered as a promising molecular target with its inhibition and a novel therapeutic strategy for the treatment of T2DM by enhancing insulin sensitivity in various cells[197]. Several PTP1B inhibitors have already been discovered, which act by interacting with the binding site of the enzyme surrounding the catalytic amino acid Cys215 and the neighboring area or with the allosteric site around Phe280[198]. PTP1B inhibitors improve the sensitivity of insulin receptors and have the potential to cure IR-related diseases. A large number of PTP1B inhibitors, either synthetic or isolated as bioactive agents from natural products, have developed and investigated for their ability to stimulate insulin signaling[198-202].

PTP1B inhibitors enhance sensibility to insulin by restricting the activity of enzyme and have curing effects. These promising advantages stimulate enormous efforts in PTP1B drug discovery from natural products, synthetic heterocyclic scaffolds, or heterocyclic hybrid compounds. Various protocols are being formulated to boost the pharmacological effects of PTP1B inhibitors. Moreover, the new advancements suggest that it is possible to obtain small-molecule PTP1B inhibitors with the required potency and selectivity[203]. Furthermore, future endeavors *via* an integrated strategy of using medicinal chemistry and structural biology will hopefully result in potent and selective PTP1B inhibitors as well as safer and more effective oral drugs.

At present, however, the structural homologies in the catalytic domain of PTP1B with other protein tyrosine phosphatases (PTPs) like leukocyte common antigen-related, CD45, SHP-2 and T-cell-PTP post a challenge to achieving selectivity. Thus, only highly selective molecules exhibiting desired effects with minimal side-effects may find their clinical application.

4.3 ARIs

Although careful control of glycemia and blood pressure can effectively stabilize or even decrease morbidity and mortality associated with diabetes, existing cardiovascular complications may or may not be effectively relieved. The polyol pathway is of prime importance in the pathogenesis of diabetic complications. Aldose reductase (AR) is an enzyme of aldoketo reductase superfamily that catalyzes the conversion of glucose to sorbitol in the polyol pathway of glucose metabolism, whose activation under hyperglycemic conditions leads to the development of chronic diabetic complication, and inflammatory and cytotoxic conditions, even under a normoglycemic state[204-205]. AR represents an excellent drug target, and in this context, ARIs have received much attention worldwide. Diminishing sorbitol flux through suppressing polyol pathway by ARIs is an emerging approach for the management of major complications of diabetes.

Indeed, a huge effort has been made to disclose novel compounds able to inhibit AR. Several ARIs with the potential, supported by promising pre-clinical results, to address diabetic complications and inflammatory diseases are being developed lately. Natural compounds and plant extracts are the major resources of ARIs[205-206]. In addition, a variety of synthetic small molecules as well as natural compounds were reported to inhibit AR. The chemical structures of ARIs are diverse, although carboxylic acid derivatives are the most important and the largest class of ARIs due to the structural feature of carboxylate anion group which fits well in the active site of AR. ARIs developed to date vary structurally and can be grouped into the following subclasses accordingly: (1) acetic acid derivatives (epalrestat, alrestatin, zopalrestat, zenarestat, ponalrestat, lidorestat, and tolrestat), (2) cyclic amides (sorbinil, minalrestat, and fidarestat), and (3) phenolic derivatives (related to benzopyran-4-one and chalcone). Among these inhibitors, epalrestat is the only commercially available inhibitor till date in Japan and recently permitted for marketing in China and India for the treatment of diabetic complications[207-208]. In addition, some other ARIs such as sorbinil and ranirestat have been advanced into the late phase of clinical trials and found to be safe for human use. Several structurally diverse chemical classes including

carboxylic acid derivatives and cyclic imides have been explored as ARIs and are being used in a number of disease conditions like inflammation, asthma, uveitis, cancers and diabetic complications as well[209-210].

Apart from diabetic complications, an excess of AR is found in various human cancers, such as liver, colon, breast, and cervical cancer. ARIs have been reported as safe anti-inflammatory drugs. It is believed that use of ARIs could relieve some of the major health concerns such as diabetic complications, cancer, and cardiovascular diseases.

4.4 G protein-coupled receptor agonists

G protein-coupled receptors (GPCRs) in the gut-brain-pancreas axis are key players in the postprandial control of metabolism and food intake. Human islets express nearly three hundred GPCRs, and many of them (more than 30 GPCRs) have been implicated in the development and progression of β-cell dysfunction, IR, obesity, and inflammation, which can lead to T2DM[211-213]. Because of the critical pathophysiological function of GPCRs in the context of diabetes, they have been be taken as new therapeutic targets for the treatment of T2DM[214-215]. Pharmaceutical companies are developing T2DM therapies that activate islet GPCRs, that is, GPCR agonists, including the incretin receptors (GLP1R, GIPR), GPR119, FFAR1 (GPR40), FFAR4 (GPR120) and the bile acid receptor GPBAR1 (TGR5)[215-217]. Yet, to date GLP-1 receptor is the only islet GPCR for which agonists are in current clinical use, as already described in a previous section. A number of small-molecule GPR119 agonists have been developed as new oral antidiabetic drugs, aiming to enhance insulin secretion and reduce appetite by targeting gut endocrine cells alongside pancreatic β-cells. Such agonists are thought to have a low risk of inducing hypoglycemia and a beneficial impact on body weight. Several GPR119 agonists have entered clinical studies; however, despite good evidence of efficacy in preclinical studies with animal models, they failed to yield metabolic benefits in humans with T2DM[218]. Hence, many of these compounds have failed either in phase I or II and none has progressed beyond phase II[216].

It was therefore proposed that highly desirable properties for new GPCR agonists would include: Gαs- or Gαq-coupled receptor activity on pancreatic β- and δ-cells, low receptor activity on α-cells, high activity on GLP-1-producing L cells and direct central nervous system effects to reduce food intake[215].

4.5 Anti-diabetic phytochemicals

We have witnessed a growing body of evidence from animal studies supporting the anti-diabetic properties of some dietary polyphenols as a dietary therapy for the prevention and management of T2DM. Commonly consumed dietary polyphenols include polyphenol-rich mixed diets, tea and coffee, chocolate and cocoa, cinnamon, grape, pomegranate, red wine, berries, and olive oil. Dietary polyphenols may inhibit α-amylase and α-glucosidase, glucose absorption in the intestine by sodium-dependent glucose transporter 1 (SGLT1), and hepatic glucose output and stimulate insulin secretion. Polyphenols may also enhance insulin-dependent glucose uptake, activate 5' AMPK, modify gut microbiome, and elicit anti-inflammatory effects. However, human epidemiological and intervention studies showed inconsistent results[219]. These facts prompted us to propose that discovery and development of single-compound natural products (NPs) with clear bioactivities might be the right way to go for exploring new natural anti-diabetic therapeutics. Indeed, NPs, particularly traditional herbal medicine and medicinal plants, have become an important resource of novel agents for drug discovery and have been extensively investigated for their anti-diabetic efficacy and potential clinical application to T2DM.

The mechanisms of actions of the anti-diabetic NPs identified thus far are diverse, including inhibition of intestinal α-glucosidase and α-amylase, oxidative stress protection, formation of advanced glycation end products, aldose reductase, plasma glucose levels, enhancing enzyme activity of hexokinases and glucose-6-phosphate (G6P), postprandial hyperglycemia, the activity of G6P, and the level of skeletal hexokinases and increases in the synthesis and release of insulin and glucose transporter type 4 (GLUT4), *etc*.

Kim *et al.*[219] and Hung *et al.*[220] provided an excellent and more detailed review on NPs and anti-diabetic therapy. Here we are just giving a few examples of well-known single-compound NPs for their possible applications to T2DM.

4.6 Resveratrol

Resveratrol is a non-flavonoid polyphenol that naturally occurs as phytoalexin, with the shell and stem of Vitis vinifera L (Vitaceae) as the richest source. Numerous experimental studies and clinical trials have documented the effectiveness and potential of resveratrol to benefit DM patients with reduction of blood glucose, improvement of insulin sensitivity and preservation of pancreatic β-cells, as well as alleviation of diabetic complications[221-222]. The therapeutic action and mechanisms of this compound on diabetes are complex and multifaceted. It has been speculated that use of resveratrol, alone or in combination with current anti-diabetic agents, might be a better approach for more effective management of DM and associated complications in the future[221,223]. However, a recent meta-analysis on three RCTs with a total of 50 participants did

not reach a conclusion as to whether resveratrol is beneficial or adverse following 4-5 weeks treatment at 10 mg to 1 000 mg T2DM patients due to inadequate evidence[224].

4.7 Curcumin

Curcumin is a bioactive constituent present in the rhizome of the Curcuma longa plant, also known as turmeric. It has been reported to retard the development of diabetes, improve the function and prevent death of β-cells, and decrease IR[225]. The anti-diabetic activity of curcumin was also attributed to its potent suppressive effects on oxidative stress and inflammation. Moreover, it can also ameliorate the diabetes-induced endothelial dysfunction and downregulate the expression of nuclear factor-kappa B. Furthermore, curcumin has also been demonstrated to inhibit advanced glycation and collagen crosslinking[226]. A randomized, double-blinded, placebo-controlled trial including 240 prediabetic subjects showed that after curcumin (curcuminoids 250 mg/day) or placebo capsules for 9 months, none of subjects were diagnosed with diabetes, whereas 16.4% of the placebo group were diagnosed with T2DM[227]. A more recent study reported that curcumin supplementation (475 mg) for a period of 10 days attenuated hyperglycemia and hyperlipidemia in T2DM subjects treated with glyburide[228].

4.8 Berberine

Berberine, an isoquinoline alkaloid extracted from Coptis Root and Phellodendron Chinese, has been used as an adjuvant treatment of T2DM, hyperlipidemia, and hypertension in China. Animal and human studies have demonstrated this compound as a hypoglycemic agent in the management of diabetes[229-230]. A systemic review on 27 randomized controlled clinical trials with a total number of 2 569 patients revealed that berberine has comparable therapeutic effect on T2DM, hyperlipidemia and hypertension without serious side effect[231]. Another meta-analysis with 28 clinical studies of 2 313 T2DM patients focusing on fasting plasma glucose, postprandial plasma glucose and HbA1c levels suggests that the anti-diabetic efficacy of berberine combined with hypoglycemics is better than that with either berberine or hypoglycemics monotherapy[232]. Evidence has been presented that berberine lowers blood glucose in T2DM patients through increasing insulin receptor expression[233].

5 Conclusions and perspectives

In summary, T2DM is a heterogeneous and progressive systemic condition that represents a series of metabolic disorders characterized by hyperglycemia and caused by defects in insulin secretion and/or insulin action due to a complex network of pathological processes. It is driven by multiple genetic and environmental factors that interact and mutually reinforce one another leading to an increased risk of complications including heart, peripheral arterial and cerebrovascular disease, obesity, and nonalcoholic fatty liver disease, among others. At present, T2DM has become the third leading cause of human death. Studies have shown that the risk of death and cardiovascular events in diabetic patients is 1.5-2.0 times higher than that in healthy people[234-235].

Although T2DM can be treated by a decent array of drugs, current pharmacologic therapy is not enough: straight glycemic control with neither cure of the disease per se nor effective prevention of associated complications. Even the control of blood sugar level is not as idea as we expect or as it should be, and sometimes the side effects elicited by the anti-diabetic drugs overwhelm their beneficial effects. Despite that intensive and extensive research has let identification of a large body of potential therapeutic targets for T2DM, agents with precise and specific targeting or alternatively broad-range targeting, on the key factors or pathways leading to the disease and its complications are presently lacking. For example, while it has been known that IR is a key element of T2DM, none of the market drugs targets the enhancement of the action of the intracellular part of insulin receptor or recuperation of the glucose transport mechanism in GLUT4-dependent cells. This situation can be partly ascribed to our insufficient understanding of etiopathogenesis and mechanisms of T2DM. Clearly, there is still a need to identify additional therapeutic agents for better management of the disease and its complications.

While there is nothing wrong for aiming to achieve optimal glycemic control, because uncontrolled glucose levels result in T2DM progression and increase the risk of complications and mortality, such a strategy often increases the risk of hypoglycemia. Several antihyperglycemic agents have been developed over time, which provides us an opportunity for prescribing anti-T2DM agents based on suitability for the individual patient's characteristics. Yet our poor understanding of pharmacogenetics, the branch of genetics that investigates how our genome influences individual responses to drugs, therapeutic outcomes, and incidence of adverse effects, prevents us from taking benefits. According to a systemic review, there are 40 polymorphisms for each drug class among metformin, DPP-4 inhibitors/GLP1R agonists, thiazolidinediones, and sulfonylureas/meglitinides[236]. This finding suggests the possibility of genetic screening of variants/loci for identifying the precise therapeutic targets and for decision-making on the therapeutic approach through precision medicine. Such an approach is anticipated to improve the efficacy and safety of anti-diabetic pharmacotherapy of T2DM on one hand and to reduce the economic burden on a global scale on the other hand.

Some therapies for diabetes increase the risk of hypoglycemia, in particular all insulins and insulin secretagogues, including the glinides and sulfonylureas. Hypoglycemia remains a major limiting factor to successful glycemic management, despite the availability of prevention options such as insulin analogues, continuous glucose monitoring, insulin pumps, and dogs that have been trained to detect hypoglycemia. It is often necessary to rely on combination therapy of multiple drugs or insulin. For example, combination treatment with a GLP-1 agonist and basal insulin has been proposed as a treatment strategy for T2DM that could provide robust glucose-lowering capability with low risk of hypoglycemia or weight gain. GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycemic control with no increased hypoglycemia[237]. However, combination drug therapy bears some inherent challenges, *e.g.*, different agents with different pharmacokinetics that are not easy to mutually compromise, possible drug interactions, difficulty of determining optimal dosages, *etc*. A superior approach that could avoid the weaknesses of combinational drug therapy is the one based on the idea of "one drug-multiple targets"[238-240] or polypharmacology[241], a new subdiscipline of pharmacology for the design or use of pharmaceutical agents that act on multiple targets or disease pathways. Whilst there have not been any rationally designed multitarget drugs for diabetes, "one drug-multiple targets" or polypharmacology would be a right direction for our future endeavors for the cure of T2DM and its complications.

An exciting part of the findings from basic research is the identification and characterization of the primary pathophysiological factors as the potential therapeutic targets for T2DM and its complications in addition to deficient insulin secretion and IR[242]. Evolving findings unravel the critical roles of glucose transport, adipokine dysregulation, immune deregulation, chronic/low-grade inflammation, gut microbiota anomalies, and mitochondrial dysfunction in the pathogenesis and progression of T2DM and its associated complications. These findings lay the groundwork for future development of new agents that specifically and precisely act on one of the newly identified therapeutic targets or that integrate appropriate elements for multiple targeting based on the principle of polypharmacology.

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Conflicts of interests

All authors declare no competing interests.

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